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Hereditary Ataxia

A Survey of Certain Clinical, Pathologic and Genetic Features with Linkage Data on Five Additional Hereditary Factors

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INTRODUCTION

THE clinical and pathologic features of an ataxia transmitted as a dominant hereditary trait in a six generation family of 343 members have been described in two previous papers (Schut, 1950; Schut & Haymaker, 1951). It is the purpose of this paper to review certain genetic features which were not discussed in the reports mentioned, and to list data assembled on certain other inherited factors, namely, the blood groups and the ability to taste phenylthiocarbamide.

The large size of the family with this hereditary trait offers several unique opportunities for study. It has been possible to observe differences of expression as a result of the appearance of the trait in distantly related branches of the pedigree, and to define some constant clinical and pathologic features. In the past certain of these differences of expression have been attributed to multiple alleles or to mutations of different genes. In this pedigree it is possible to ascertain what part of the variation is due to genetic and/or environmental modification.

The pedigree chart of this kindred is presented in figure 1. In previous papers, the author used the usual method of designating individual members by generation and serial numbers (e.g. *V-6*). In the present paper, a method introduced by Cotterman and Falls (1944) is employed. Each sibship is assigned a number on the chart, and the individual is identified by this number and by the birth order within the sibship. The propositus for this investigation is the affected male *16-2*.

The trait could be traced to an ataxic male of Dutch ancestry who migrated with some of his daughters to northwestern Iowa in 1866. Most of his descendants live in that general area today, and in adjacent areas of South Dakota and Minnesota. His ataxic brothers and one ataxic daughter remained in the

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Netherlands, but it has been impossible to determine whether these three affected men had children. For this reason there may be a connection between this family and others whose origin has been in the Netherlands. Dr. J. van den Bosch, Balkburg, Netherlands has recently sent me a report of the neurologic examination of *19-3*, who resides in Zwolle, Netherlands.

In 1915, when *3-7* and *3-8* were becoming ataxic, they went to the Mayo Clinic, Rochester, Minnesota, where they received the diagnosis of family ataxia. Until this time they had not identified their disorder with the disease from which their mother had died. When the children of these two members became affected, they came to the University of Minnesota Hospitals, where a provisional pedigree was formulated, and the diagnosis confirmed. In 1939, when *16-2* died, Drs. R. C. Gray and C. P. Oliver (1941) compiled the available genetic material, and presented a clincopathologic report of the case. Subsequently the author extended these studies at the Institute of Neurology, Northwestern University Medical School, Chicago, Illinois, and the Armed Forces Institute of Pathology, Washington, D. C.

GENERAL CLINICAL FEATURES

Age at onset. The early symptoms and signs were intermittent, thus the age of onset was particularly difficult to ascertain with accuracy. The age of onset was obtained for 32 members, usually within a range of years (table 2, column 12). These ranges were used in computations regarding age of onset.

In 31 instances definite symptoms of ataxia appeared before the age of 35; in only 1 was onset between 35 and 40 years. The earliest age of onset for any member (*21-5*) was 17, and the average was 26.5 years for the 32 members on whom such information was obtained.

The average age at onset for the 7 members of generation *III* was 29.20 years; for 20 members of generation *IV*, 26.85; and for 5 members of generation *V*, 21.6. In spite of the fact that ranges instead of exact ages were used, this drop in the average age of onset from one generation to the next appeared to be statistically significant. Nevertheless the number of children of each affected parent in whom ataxia developed at a younger age than it had in the parent was equaled by the number in whom onset was at a later age. Furthermore, there was little correlation between parent and child or between siblings with regard to age at onset. Had a high correlation between parent and child existed, the average age at onset would tend to rise with each generation rather than to fall, because those in whom the disease developed later in life would be more likely to reproduce and have larger families before disability set in or death occurred.

Certain observations might be advanced in explanation of the relatively small differences that existed in average age at onset between the generations.

(1) The recording of members having a younger age of onset. In generation *IV* there are 8 members past the age of 28 years and under 35 who may yet develop ataxia. If any of these 8 members become ataxic in the future, the average age at onset for that generation would be raised, and a smaller difference would exist between the third and the fourth generations. The same applies to generation *V* where the trait may yet appear among the many young members as they pass through the critical age period.

(2) The assignment of older ages at onset to members of generation *III*. The current method of determining the time at which the disease commences is to ascertain by examination the presence of a group of signs and symptoms. The age at onset determined by this method is usually earlier than the age at which the patient himself admits the presence of the disease. Since all affected members of generation *III* were deceased when this study was begun, the ages at onset were secured from the spouses or associates, and obtained in this manner were probably somewhat higher than those at which symptoms actually appeared. It is obvious that this pedigree would not have attained such a size had members of the first and second generation exhibited ataxia early in life.

Duration. In 21 instances in which both age at onset and age at death were known, the average duration of the ataxia was 10.2 ± 4.6 years,[2] the range extending from 1 to 22 years. Duration was influenced significantly by intercurrent infections and the time at which bulbar symptoms appeared. Possibly these two factors concealed a real correlation between age at onset and age at death, for when the members having an obvious cause for early or late death were excluded, there appeared to be a tendency for those developing the disease early in life to have it for a shorter period of time.

Age at death. The age at death averaged 36.8 ± 6.4 for 27 deceased members (10 men, 39.6 ± 6.5; 17 women, 35.2 ± 5.8). The same factors which influenced the duration of the disease were operative here. Data on generations *II* and *III* are complete; age at death for the four women of *II* averaged 42.0 ± 6.0, for 8 ataxic members of *III*, 39.1 ± 4.7. The lower age of death in members of the next two generations, especially the striking drop between generations *IV* and *V* (*IV*, 35.8 ± 5.5 in 11 members; *V*, 27.3 ± 3.2 in 3 members), probably has the same causation regarded as responsible for antedating in data on age at onset. More recently the modern antibiotics have served to prolong the lives of many of the living ataxic members.

NEUROLOGIC FEATURES

The neurologic manifestations of the ataxia were particularly diverse. Twenty-two affected members were examined, 13 by me and 9 by others.

[2] Quantities following the ± sign are standard deviations in this section.

For purposes of study, they were divided into 4 groups on the basis of definite clinical criteria. The previous clinical report (Schut, 1950) detailed four representative cases, one from each clinical category. The four disease forms were: Friedreich's ataxia, 1 case; hereditary cerebellar ataxia, subgroup A, 7 cases;

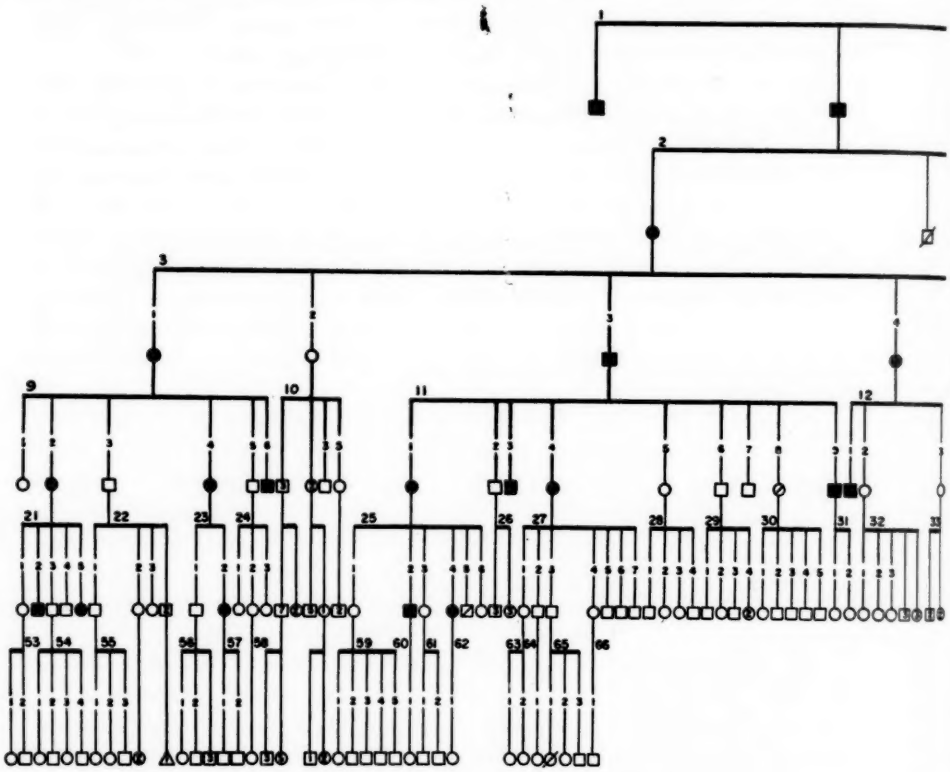


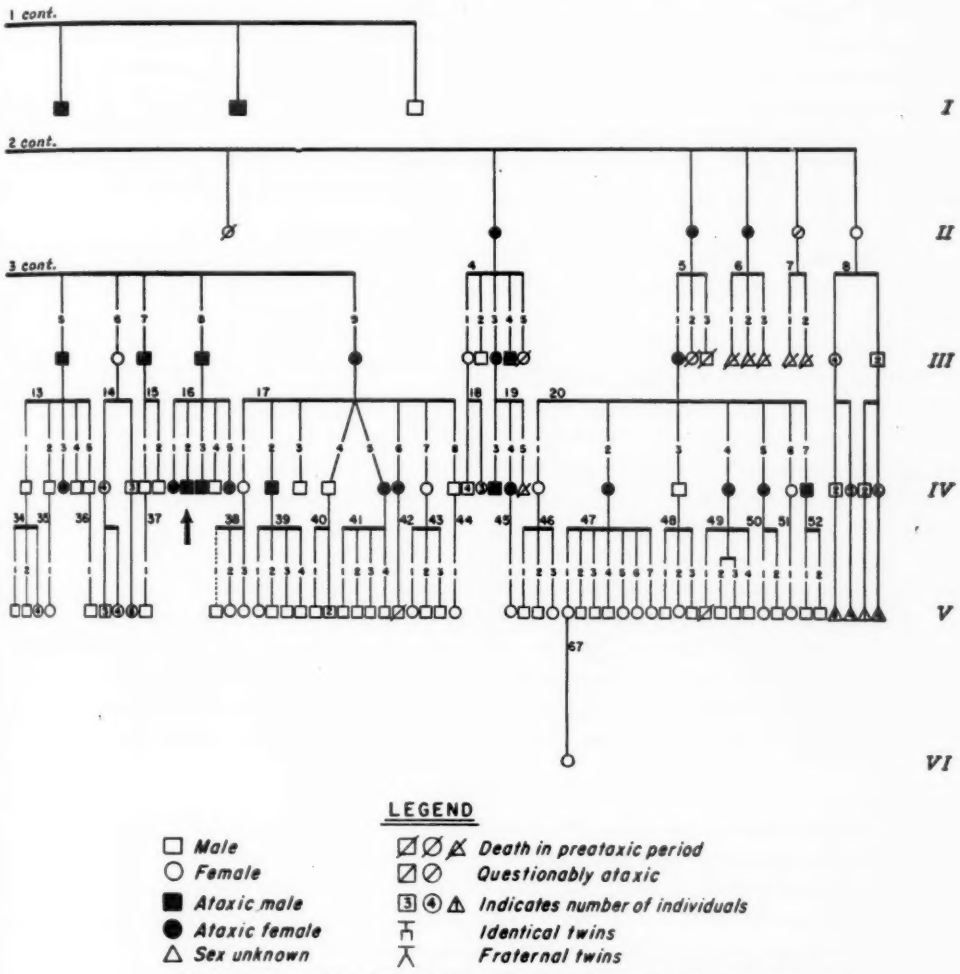
FIG. 1. PEDIGREE CHART OF A FAMILY DISPLAYING HEREDITARY ATAXIA.

This chart, Armed Forces Institute of Pathology Negative No. 195109, is based upon all information available in April, 1948. On a recent field trip (July, 1950) it was observed that *11-8*, *13-5* and *27-3* showed first signs of ataxia; *25-5*, labelled here as questionably affected, was not ataxic. This new information, not shown in the figure, has been incorporated into table 2, but the necessary revisions in the partial sex-linkage test (table 1, addition of 1 cross-over, *13-5*) and other statistics of the paper have not been made.

hereditary cerebellar ataxia, subgroup B, 12 cases; hereditary spastic paraplegia, 2 cases. These syndromes which appeared in members of a family stemming from a common ancestor have heretofore been recognized as separate clinicopathologic entities. The demonstration of their similar origin constitutes evidence for the hypothesis that in many instances the three diseases are basically similar processes.

PATHOLOGIC FEATURES

A pathologic study of 5 cases from this pedigree (*9-6*, *11-3*, *16-1*, *16-2*, *21-5*, seen on the genealogic chart of previous articles as *IV-6*, *IV-9*, *IV-26*, *IV-27*, *V-5*) showed that the nuclear structure most consistently affected was the inferior olivary nucleus. In case *21-5* with the clinical diagnosis of Friedreich's disease, posterior column degeneration and olivopontocerebellar atrophy were very severe and changes in the bulbar cranial nuclei were prominent. In



9-6, a case which represented hereditary cerebellar ataxia (subgroup A) in the clinical classification, only mild to moderate posterior column degeneration was observed, but there was severe cortical cerebellar atrophy combined with olivopontocerebellar atrophy. The three other cases (*11-3*, *16-1*, *16-2*) had been classified hereditary cerebellar ataxia (subgroup B) on the basis of clinical features. Pathologically, posterior column degeneration was absent in *16-2*, mild in *16-1*, and severe in *11-3*. In these cases shrinkage of the cerebellum was minimal and microscopic changes in the structure were slight in *16-1*, but were moderately advanced in *11-3* and *16-2*.

Degenerative changes in the bulbar nuclei confirming clinical evidence of bulbar palsy were prominent in *21-5* and *16-1*, but were only moderate in *11-3* and *16-2* and minimal in *9-6*.

The spinal cord was available for study in only 2 cases, *9-6* and *16-1*, and in both of them the anterior horn cells exhibited severe degeneration.

The varying degrees of degeneration of the posterior columns may have been the result of the differences in duration of the disease, for clinically *11-3* had no evidence of affection of the posterior columns when he was examined 11 years after the onset. In 9 other members of this subgroup who were examined in a similar stage of disability no neurologic signs of posterior column affection appeared until the late stages of the disease. However certain members of subgroup A manifested definite signs of posterior column involvement before they had had the disease for as much as 10 years.

In summary, the structures of the central nervous system involved in the degenerative process in this family were: 1) the posterior columns and roots of the spinal cord, 2) the cerebellum with its afferent and efferent pathways, 3) the lower motor neuron system in the bulb and spinal cord, and 4) the pyramidal system. While there is no pathologic evidence that the pyramidal system was involved, certain living members (*17-2*, *16-3*, *20-2*) now display definite clinical signs of advanced degeneration in this system.

Localization of the Degenerative Process

A well established principle which emerged in the clinical and pathologic studies was that there was considerable variation in the site of the degenerative process. The major changes remained limited to the four systems enumerated, but it was noted that while one member might have severe degeneration in one system, in another the same system might have escaped entirely. Comparison of *21-5* (onset at 17 years, death at 25) with *16-2* (onset at 20 years, death at 30), affords the best example of this phenomenon. In *21-5* degeneration of the posterior columns was striking, while in *16-2* the posterior columns were unaffected even though the age of onset of ataxia and duration of the disease were essentially similar. An analogous difference in localization was observed in reference to the degenerative process in the pons

and its afferent pathway to the cerebellum in the brachium pontis, which was severe in *21-5* and minimal in *11-3*, *16-1* and *16-2*.

The familial nature of these differences in localization was shown by the clinical study. The progeny of *3-1*, consisting of *9-2*, *9-4*, *9-6*, *21-2*, *21-5*, and *23-2*, all showed clinical evidence of early posterior column degeneration, without involvement of the pyramidal system. On the other hand, *5-1* and her 4 ataxic children (*20-2*, *20-4*, *20-5*, and *20-7*) had early signs referable to the pyramidal system, and in those examined symptoms of involvement of the posterior columns have not been detected late in the course of the disease.

Thus there appeared to be a modification of hereditary type which produced differences in localization of the degenerative process. It was interpreted as genetic modification. Although the mutant dominant gene must be present to determine the existence of the disease, the exact localization of the degenerative process within the systems seems to be dependent upon other genes inherited separately.

GENETIC FEATURES

The trait is obviously a dominant with 100 per cent penetrance, for the presence of the ataxia in every member depended upon the disease in one parent (the affected parent in generation *I* is unknown). Tallying of the frequencies of the affected and normal children of ataxic individuals, separated as to sex, shows that the ratio does not depart significantly from a 1:1:1:1 ratio (affected males: unaffected males: affected females: unaffected females = 16:19:21:16). Progeny of unaffected members (*2-8*, *3-2*, *3-6*, *9-3* and *1-5*) number 200 or more and have been recorded with reasonable accuracy. Many other members are well past the age at which the ataxia usually occurs (*9-1*, *9-5*, *11-2*, *13-1*, etc.), are normal, and have healthy children. Knowledge of complete penetrance of the gene and of a maximum age of onset have been particularly helpful in counseling many members of this family.

Partial Sex-Linkage

A dominant partially sex-linked character received by an affected man from his mother tends to be transmitted to his daughters; one received from his father tends to appear in his sons. The evidence for inheritance of this type in this pedigree is not conclusive, but is presented in table 1.

It will be noted that sibship *2* is included in this tally although the affected paternal grandparent is not known. Assuming this to be the grandmother, we would have $P = 0.017$ for the (exact binomial) probability of a deviation as large as or larger than 17:6. Omitting this sibship, we have the ratio 13:5, with $P = 0.048$. Conclusive evidence for partial sex-linkage must therefore await the time when *13-4*, *13-5*, and *15-2* are past the upper limit of the age at onset (their ages in 1950 being 30, 28, and 33 years, respectively). Should

they remain free from the ataxia, it will furnish further information for the phenomenon of partial sex-linkage, as would the determination of the affected parent of generation *I*. In the determination of partial sex-linkage, it would also be constructive to know the genotype of the children of *25-2*, *17-2*, and *20-7*, but because of their age it will be some time before their status as regards the ataxia can be accurately assessed. The data also appear to be affected by the preponderance of women in generation *II*; furthermore the seemingly significant preponderance of males in generation *V* may possibly enter into future computations on partial sex-linkage.[3]

Haldane (1941*a*) has shown that the determiner for recessive spastic paraplegia is a partially sex-linked gene. He submits evidence elsewhere (1941*b*), however, that this disease is different from the spastic paraplegia determined

TABLE 1. SIBSHIPS SUPPLYING INFORMATION RELATIVE TO HYPOTHESIS OF PARTIAL SEX-LINKAGE

SIBSHIP	FATHER	SEX OF AFFECTED PATERNAL GRANDPARENT	MALES		FEMALES	
			Affected	Unaffected	Affected	Unaffected
2	*1-2*	Unknown	0	0	4	1
11	*3-3*	Female	2	3	3	1
13	*3-5*	Female	0	2*	1	0
15	*3-7*	Female	0	1†	0	0
17	*3-8*	Female	2	1	2	0
Totals			4	7	10	2

* Two additional unaffected males, *13-4* and *13-5*, are still within the age of onset period.
† One additional unaffected male, *15-2*, is still within the age of onset period.

by a dominant gene, which appears as an autosomal trait. This partially sex-linked recessive form of hereditary spastic paraplegia is probably different from the form which has also appeared in members of this series.

Bell and Carmichael (1938) reviewed most of the reported cases of ataxia, along with those of hereditary spastic paraplegia. They separated hereditary ataxia into two groups, using the presence or absence of the knee jerk as the sole criterion. They designated the group without this deep reflex as Friedreich's disease, with the reflex as spastic ataxia. Among many comparisons made between these two arbitrary types of ataxia, they showed that spastic ataxia was more often dominant than the Friedreich form. Sjögren (1943) reviewed a large group of ataxics in Sweden, and although he accepted the recorded diagnoses, he concluded that both a dominant and a recessive form of the disease existed. Leers and Scholz (1939) in their extensive review maintain that there is no particular difference in mode of inheritance between the

[3] A provisional pedigree of a large Dutch family with hereditary ataxia, sent to me by J. van den Bosch, Balkburg, Netherlands, shows a similar tendency in favor of partial sex-linkage. However, the gene for the disease in this family does not appear to be 100 per cent penetrant in heterozygotes.

two forms of the disease. The lack of definite clinical criteria to distinguish these forms of hereditary ataxia is the most probable explanation for the differences in interpretation as to mode of inheritance.

Brain (1925) also sought to explain the type of heredity in ataxia. He noted that the disease often appeared in members whose parents were apparently normal (Brown, 1892; Triebel, 1922). In explanation he postulated that the dominant gene could not produce the disease unless assisted by a homozygous set of accessory genes. Heredity of this type allowed for latent forms of the disease, and the appearance of the ataxia would be dependent in part upon the genetic make-up of the mate. Popenoe and Brousseau (1932) thought that the modifiers were responsible for alterations in the expression of the mutant gene, causing the apparent change in penetrance and anatomic localization of the degenerative process. The authors extended their theory in an effort to explain abortive forms. However, the phenomenon of multiple allelism has been evoked to explain variation that exists between members of separate ataxic families. In studies of this nature it is possible to secure information on the extent to which genetic and/or environmental modification is responsible for variation.

Linkage with Test Factors

If a tight linkage could be found between the dominant gene for hereditary ataxia and some other gene invariably expressed at an early age it would be of great value in counseling members of the family who might later develop this disease. However, if crossing-over occurs with a frequency of more than 10 per cent, the value of the linkage would be limited. It is the appearance of the ataxia in this family after the age of 20, and the existence of 59 members who by virtue of their parentage may exhibit the trait before the age of 35 that make the effort to discover linkage of particular value in prognosis. In the presence of proved linkage relationships such a study as this will also aid in genetic classifications and assist in formulation of concepts relating to the heterogeneous origin of hereditary ataxia.

Because the definite inheritance of the blood groups is well established, a possibility existed that a study of blood groups in members of this family might reveal linkage with the gene for ataxia.[4] In addition to ABO, Rh, and MN systems, a recently discovered antigen, Kell, was tested in this study. It was first reported by Coombs, Mourant and Race (1946) who gave it that designation. In 1947 it was independently described by Wiener who called it Si. The identity of the two was brought out by Sanger, Bertinshaw, Lawler and Race, in 1949, in a study of 423 Caucasian bloods; these investigators

[4] If the gene for ataxia in this kindred should be regarded as incompletely sex-linked, this might be thought to make unnecessary tests for linkage with the ABO, MN, Rh, or K genes, since evidence for incomplete sex-linkage of these serological factors is wanting. However, any of the latter might ultimately prove to be loosely linked with sex, so that tests for linkage between ataxia and the antigenic factors would not be amiss.

also emphasized the dominant behavior of the antigen. They estimated gene frequencies as $k = 0.9478$, $K = 0.0522$. Levine and associates (1949) have described an antigenic factor to which they gave the name Cellano; it is present in 99.8 per cent of all bloods and is due to an allele (k) of the Kell gene (K).

Materials and Methods. The blood for typing was obtained on a tour made through areas of the Middle West where members of this family were residing. Blood was drawn in sterile vacuum syringes and sent to the Blood and Blood Products Division of the Research and Graduate School, Army Medical Center, Walter Reed Hospital, Washington, D. C. The clotted specimens were sent by Air Express and were received about 24 hours after they were sent. They were refrigerated until morning, and when the tests were made all specimens were considered to be in good condition. All antisera used were known to be specific and of good potency.

Tests were made for ABO and MN blood factors, for Rh_0 (D), rh′, (C), rh″ (E), Hr′ (c) types, and for the Kell antigen. Dr. Wiener was kind enough to supply sufficient antisera to determine the distribution of Kell in this family. Clinical tests were also made to determine the ability of members of the family to taste phenylthiocarbamide, a character which is also known to follow a definite hereditary pattern.

Ideally the study should be carried out by utilizing the refined methods developed by Norton (1949), but contemplation of the material shows that while such a study would increase the efficiency of utilization of the data, it would not sharpen the picture sufficiently from the point of view of counseling to make the expenditure of effort worthwhile. Nevertheless the material is recorded in table 2 for utilization by those interested in future studies.

Results. The critical matings supplying information on linkage are listed below. There is no proof of linkage in any case, though the data are not sufficient to disprove the possibility. They do show that if linkage exists it is too weak to be of great practical value.

1. Kell (Si) antigen. The critical matings involve children of *3-5*, *3-8*, *9-2*, *9-4*. Minimum possibility of 3 crossovers among 12 individuals.

2. ABO blood group. The critical matings involve children of *11-1*, *3-5*, *5-1*. Minimum possibility of 5 crossovers among 10 individuals.

3. Rh blood types. The critical matings involve the children of *11-1* (for *e*). Minimum possibility of 2 crossovers among 4 individuals.

4. MN blood types. The critical matings involve children of *3-8*, *5-1*. Minimum possibility of 2 crossovers among 9 individuals.[5]

5. PTC taste ability. The critical matings involve children of *11-1*.

[5] The children of *3-8* and *5-1* are second cousins, and if crossing-over had taken place in *3-8* or her mother, we should expect the ataxia gene to come in with the N instead of the M as we have assumed in the case of *5-1* and her children. The ratio would then be 8:1 instead of 7:2. This is but one inherent difficulty in scoring separate sibships of a single pedigree where there is possibility of loose linkage relationships.

TABLE 2. TEST FACTORS AND OTHER MISCELLANEOUS DATA ON A KINDRED EXHIBITING HEREDITARY ATAXIA

Each sibship is separated by a horizontal line; the parents are listed at the bottom of each sibship and are indicated by an asterisk (*) preceding the entry. Data enclosed in square brackets [ ] are phenotypes inferred from those of the spouse and children. Missing data are indicated by double dots (..). The diagnosis of ataxia (H or h) is omitted for all unaffected individuals who have an affected parent but are under 35 years of age.

The columns of data represent: (**1**) individual number, corresponding to the pedigree, Fig. 1; the letter *a* following a number designates the spouse; (**2**) sex; (**3**) H = heterozygous for hereditary ataxia, h = normal; (**4**) Kell (Si) blood type; (**5**) ABO blood group; (**6**) Rh_0 (D); (**7**) rh′ (C); (**8**) rh″ (E); (**9**) Hr′ (c); (**10**) MN blood type; (**11**) T = taster, t = non-taster of phenylthiocarbamide; (**12**) age at onset, expressed as a range in years; and (**13**) date of birth (month-day-year).

1	2	3	4	5	6	7	8	9	10	11	12	13
3-1	F	H	..	..	..	..	..	..	..	..	25–28	5-7-66
3-2	F	h	[+]	..	[+]	[+]	[−]	[−]	[MN]	[T]	..	1-11-70
3-3	M	H	..	..	..	[+]	..	..	..	..	28–33	1-7-73
3-4	F	H	..	..	..	..	..	[+]	..	..	30–34	9-11-76
3-5	M	H	[+]	..	[+]	[+]	..	..	[MN]	..	35–40	2-6-78
3-6	F	h	−	A_2	+	+	−	−	MN	t	..	5-3-80
3-7	M	H	..	..	..	..	..	..	..	..	30–32	10-22-82
3-8	M	H	[+]	..	..	[+]	..	..	[MN]	..	20–23	10-26-84
3-9	M	H	[+]	..	..	[+]	..	..	..	..	23–28	9-8-86
**2-1*	F	H	..	..	..	..	..	..	..	..	..	
**2-1a*	M	h	..	..	..	..	..	..	..	..	..	
5-1	F	H	..	A_1	..	[−]	..	[+]	[MN]	..	33–?	(1878)
5-1a	M	h	−	O	+	+	−	−	N	T	..	
9-1	F	h	+	A_2	+	+	+	+	MN	..	..	6-8-91
9-2	F	H	[+]	..	..	[+]	..	..	..	..	20	9-11-92
9-3	M	h	..	..	..	..	..	..	..	..	..	6-14-94
9-4	F	H	[+]	..	..	[+]	..	..	..	..	19–20	1-26-90
9-5	M	h	−	O	+	+	+	+	M	T	..	4-25-02
9-6	M	H	..	..	..	..	..	..	..	..	29–30	4-30-05
**3-1*	F	H	..	..	..	..	..	..	..	..	25–28	5-7-66
**3-1a*	M	h	..	..	..	..	..	..	..	..	..	
10-3	M	h	+	O	+	+	−	+	N	t	..	2-19-04
10-5	F	h	−	O	+	+	−	−	M	T	..	5-10-09
**3-2*	F	h	[+]	..	[+]	[+]	[−]	[−]	[MN]	[T]	..	1-11-70
**3-2a*	M	h	−	O	+	+	−	+	MN	t	..	
11-1	F	H	..	..	[+]	[+]	[−]	[+]	..	..	21	1-12-96
11-2	M	h	−	A_2	+	+	−	+	MN	..	..	6-19-87
11-3	M	H	..	..	..	..	..	..	..	..	25	5-10-99
11-4	F	H	..	..	[+]	[+]	[−]	[+]	[MN]	..	22–24	10-11-02
11-5	F	h	−	A_1	+	+	−	+	N	T	..	10-5-05
11-6	M	h	−	O	+	+	−	+	N	T	..	4-1-07
11-7	M	h	..	..	..	..	..	..	..	..	..	1-26-10
11-8	F	H	−	A_2	+	+	−	−	MN	T	34	6-18-11
11-9	M	H	−	A_2	+	+	−	−	MN	T	33	2-9-14
**3-3*	M	H	..	..	..	[+]	..	..	..	..	28–33	1-7-73
**3-3a*	F	h	..	..	..	..	..	..	..	..	..	

TABLE 2.—*Continued*

1	2	3	4	5	6	7	8	9	10	11	12	13
12-1	M	H	..	B†	..	..	..	..	..	..	25–26	11-21-02
12-2	F	h	−	A_2	−	−	−	+	MN	T	..	11-29-04
**3-4*	F	H	..	..	..	..	..	[+]	..	..	30–34	9-11-76
**3-4a*	M	h	−	A_2	+	+	−	+	MN	T	..	
† From a record of the University of Minnesota Hospitals.												
13-1	M	h	+	A_1	+	+	−	−	MN	T	..	6-5-10
13-2	M	h	+	A_1	+	+	−	−	N	T	..	4-27-12
13-3	F	H	−	A_1	+	+	−	+	MN	T	26–27	2-21-15
13-4	M		−	A_1	+	+	−	+	M	T	..	8-21-20
13-5	M	H	−	A_2	+	+	−	+	N	T	27	10-8-22
**3-5*	M	H	[+]	..	[+]	[+]	..	..	[MN]	..	35–40	2-6-78
**3-5a*	F	h	−	A_1	+	+	−	+	MN	T	..	
16-1	F	H	..	..	..	..	..	..	..	..	25	3-24-07
16-2	M	H	..	B†	..	..	..	..	..	..	20	3-17-09
16-3	M	H	−	A_1	+	+	−	+	MN	T	28–30	11-4-12
16-4	M	h	+	A_1	+	+	−	+	MN	..	..	9-16-15
16-5	F	H	−	A_1	+	+	−	−	N	T	29–30	8-16-18
**3-8*	M	H	[+]	..	..	[+]	..	..	[MN]	..	20–23	10-26-84
**3-8a*	F	h	−	A_1	+	+	−	+	MN	..	..	
† From a record of the University of Minnesota Hospitals.												
17-1	F	h	−	A_1	+	+	−	−	M	T	..	1-31-08
17-2	M	H	−	A_1	+	+	−	−	MN	T	25	9-2-09
17-3	M	h	−	A_1	+	+	−	−	M	T	..	1-15-12
17-4	M	h	−	A_1	+	+	−	−	MN	t	..	7-11-14
17-5	F	H	−	A_1	+	+	−	−	MN	T	28–29	7-11-14
17-6	F	H	−	O	+	+	−	−	M	t	32–33	12-25-15
17-7	F		−	A_1	+	+	−	−	MN	t	..	7-29-18
17-8	M		−	A_1	+	+	−	−	MN	t	..	10-7-20
**3-9*	F	H	..	..	..	[+]	..	..	..	..	23–28	9-8-86
3-9a	M	h	..	..	..	[+]	..	..	..	..	..	
20-1	F	h	−	O	+	+	−	+	N	T	..	8-28-01
20-2	F	H	−	O	+	+	−	+	MN	T	33	10-2-03
20-3	M	h	−	O	+	+	−	+	N	..	..	8-21-05
20-4	F	H	..	[A_1]	..	[+]	..	..	[MN]	[T]	30	8-24-09
20-5	F	H	..	..	..	[+]	..	..	..	..	30–32	10-15-11
20-6	F	h	−	A_1	+	+	−	+	N	T	..	1-28-15
20-7	M	H	−	O	+	+	−	+	MN	t	23–25	11-18-18
**5-1*	F	H	..	[A_1]	..	[−]	..	[+]	[MN]	..	33–?	(1878)
**5-1a*	M	h	−	O	+	+	−	−	N	T	..	
21-1	F	h	+	O	+	+	−	−	M	T	..	9-2-10
21-2	M	H	..	.	..	..	..	..	..	..	22	3-14-13
21-3	M	h	+	A_1	+	+	−	−	N	T	..	2-10-15
21-4	M	h	..	..	..	..	..	..	..	..	..	3-2-17
21-5	F	H	..	..	..	..	..	..	..	..	17	7-2-22
**9-2*	F	H	[+]	..	..	[+]	..	..	..	..	20	9-11-92
**9-2a*	M	h	−	A_1	+	+	+	+	M	..	..	

TABLE 2.—*Continued*

1	2	3	4	5	6	7	8	9	10	11	12	13
22-1	M	h	+	O	+	+	−	+	MN	T	..	..
22-2	F	h	+	O	+	−	+	+	MN	T	..	6-4-20
**9-3*	M	h	..	..	..	..	..	..	..	..	..	6-14-94
**9-3a*	F	h	..	..	..	..	..	..	..	..	..	..
23-1	F		+	O	+	+	−	−	MN	T	..	8-17-19
23-2	F	H	+	O	+	+	−	−	MN	T	25	7-22-21
**9-4*	F	H	[+]	..	..	[+]	..	..	..	..	19–20	1-26-90
**9-4a*	M	h	−	O	+	+	−	+	M	..	..	..
24-1	F	h	−	O	+	−	+	+	MN	T	..	5-8-28
24-2	F	h	−	O	+	+	−	+	MN	T	..	1-24-30
24-3	F	h	+	O	+	+	−	+	MN	T	..	3-15-34
**9-5*	M	h	−	O	+	+	+	+	MN	T	..	4-25-02
**9-5a*	F	h	+	A_1	+	+	−	+	N	..	..	..
25-1	F	h	−	A_1	+	+	−	+	N	T	..	7-3-13
25-2	M	H	?‡	A_2B	+	+	−	−	N	t	25	4-8-15
25-3	F	h	−	A_1	−	−	+	+	N	T	..	11-18-17
25-4	F	H	..	..	..	..	..	..	..	[T]	19	6-30-19
25-5	F		−	A_1	−	−	+	+	N	t	..	1-27-25
25-6	F		?	A_2B	+	+	+	+	N	t	..	3-13-25
**11-1*	F	H	..	..	[+]	[+]	[−]	[+]	..	..	21	1-12-96
**11-1a*	M	h	?	A_1B	+	+	+	+	N	..	..	..

‡ Tests for Kell (Si) were not successful when B antigen was present.

27-1	F		−	A_2	+	+	−	−	MN	T	..	8-7-25
27-2	M		−	A_2	+	+	−	−	M	T	..	3-8-26
27-3	M	H	−	A_2	+	+	−	+	M	t	21	7-4-28
27-4	F		..	..	..	..	..	..	..	..	..	3-20-29
27-5	M		−	A_2	+	+	−	+	M	T	..	9-4-31
27-6	M		−	A_2	+	+	−	+	MN	T	..	4-28-35
27-7	M		−	A_2	+	+	−	−	MN	T	..	10-26-37
**11-4*	F	H	..	..	[+]	[+]	[−]	[+]	[MN]	..	22–24	10-11-02
**11-4a*	M	h	−	A_2	+	+	−	−	M	..	..	..
28-1	M	h	−	A_1	+	+	−	−	N	T	..	7-20-25
28-2	F	h	−	A_2	+	+	−	+	N	t	..	3-12-28
28-3	F	h	−	A_2	+	+	−	+	N	T	..	9-30-31
28-4	M	h	−	A_1	+	+	−	−	N	..	..	5-30-38
**11-5*	F	h	−	A_1	+	+	−	+	N	T	..	10-5-05
**11-5a*	M	h	−	A_1	+	+	+	+	N	t	..	..
29-1	M	h	−	O	+	+	−	+	N	..	..	10-29-30
29-2	F	h	−	O	−	−	−	+	N	..	..	6-19-34
29-3	M	h	−	O	+	+	−	−	MN	..	..	2-27-38
**11-6*	M	h	−	O	+	+	−	+	N	T	..	4-1-07

TABLE 2.—*Continued*

1	2	3	4	5	6	7	8	9	10	11	12	13
30-1	F		−	A_2	+	+	+	+	MN	T	..	4-3-33
30-2	M		−	A_2	+	+	−	−	MN	T	..	7-12-34
30-3	M		−	A_2	+	+	−	−	MN	..	..	6-29-39
30-4	M		−	A_2	+	+	+	+	MN	..	..	6-15-41
30-5	M		−	A_2	+	+	+	+	M	..	..	8-29-45
**11-8*	F	H	−	A_2	+	+	−	−	MN	T	..	6-18-11
**11-8a*	M	h	−	A_2	+	+	+	+	MN	t	..	..
31-1	F		−	A_2	+	+	−	−	MN	..	..	6-15-40
**11-9*	M	H	−	A_2	+	+	−	−	MN	T	32–33	2-9-14
**11-9a*	F	h	−	A_2	+	+	−	−	MN	T	..	..
32-1	F	h	−	A_1	+	+	−	+	M	T	..	11-5-27
32-2	F	h	+	A_2	−	−	−	+	M	T	..	10-10-38
32-3	F	h	−	A_2	−	−	−	+	MN	t	..	10-19-40
**12-2*	F	h	−	A_2	−	−	−	+	MN	T	..	11-29-04
**12-2a*	M	h	+	A_1	+	+	−	+	M	T	..	..
34-1	M	h	+	A_1	+	+	−	+	N	..	..	9-9-36
34-2	M	h	−	A_2	+	+	−	−	MN	..	..	6-25-39
**13-1*	M	h	+	A_1	+	+	−	−	MN	T	..	6-5-10
**13-1a*	F	h	−	O	+	+	−	+	N	..	..	..
§*38-1*	M	h	−	A_1	+	+	−	+	MN	T	..	4-19-32
38-2	F	h	−	A_1	+	+	−	+	M	..	..	5-3-46
**17-1*	F	h	−	A_1	+	+	−	−	M	T	..	1-31-08
**17-1a*	M	h	−	O	+	+	−	+	M	..	..	..

§ Illegitimate son of *17-1*.

39-1	F		−	O	+	+	−	+	N	T	..	9-7-33
39-2	M		−	A_1	+	+	−	+	N	T	..	7-2-35
39-3	M		−	A_1	+	+	−	+	N	T	..	6-28-40
39-4	M		−	A_1	+	+	−	+	N	..	..	8-24-44
**17-2*	M	H	−	A_1	+	+	−	−	MN	T	25	9-2-09
**17-2a*	F	h	−	O	+	+	−	+	N	T	..	..
40-1	M	h	−	O	+	+	−	+	MN	..	..	10-5-44
**17-4*	M	h	−	A_1	+	+	−	−	MN	t	..	7-11-14
**17-4a*	F	h	−	A_1	+	+	−	+	MN	T	..	..
41-1	M		−	A_1	+	+	−	−	MN	T	..	6-23-39
41-2	M		−	A_1	+	+	−	−	M	T	..	9-14-40
41-3	M		−	A_1	+	+	−	−	M	T	..	6-8-42
41-4	M		..	..	..	..	..	..	..	..	..	7-12-45
**17-5*	F	H	−	A_1	+	+	−	−	MN	T	28–29	7-11-14
**17-5a*	M	h	−	A_1	+	+	−	−	M	T	..	..
43-1	F		..	..	..	..	..	..	..	..	..	7-16-39
43-2	M		?	B	+	+	−	+	N	..	..	11-12-42
43-3	M		..	..	..	..	..	..	..	..	..	11-30-48
**17-7*	F		−	A_1	+	+	−	−	MN	t	..	7-29-18
**17-7a*	M	h	?	B	+	+	−	+	N	..	..	..

TABLE 2.—*Continued*

1	2	3	4	5	6	7	8	9	10	11	12	13
46-1	M	h	−	A_1	+	+	−	−	N	T	..	4-21-26
46-2	M	h	?	B	+	+	−	+	N	T	..	5-22-28
46-3	F	h	−	A_1	+	+	−	+	N	..	..	4-14-34
**20-1*	F	h	−	O	+	+	−	+	N	T	..	8-28-01
**20-1a*	M	h	?	A_1B	+	+	−	−	MN	..	..	..
47-1	F		−	A_2	+	+	−	−	MN	T	..	7-4-26
47-2	M		−	A_2	+	−	+	+	N	..	..	1-5-28
47-3	M		−	A_2	+	+	−	+	M	T	..	2-24-31
47-4	M		−	A_2	+	+	−	+	MN	T	..	6-7-34
47-5	F		−	O	+	+	+	+	N	..	..	6-12-36
47-6	F		−	A_2	+	+	−	+	MN	T	..	2-28-38
47-7	F		−	O	+	−	+	+	N	..	..	3-29-44
**20-2*	F	H	−	O	+	+	−	+	MN	T	33	10-2-03
**20-2a*	M	h	−	A_2	+	+	+	+	MN	T	..	..
48-1	M	h	−	O	+	+	−	−	N	..	..	6-5-35
**20-3*	M	h	−	O	+	+	−	+	N	..	..	8-21-05
**20-3a*	F	h	−	O	+	+	−	−	N	..	..	..
49-2	M		−	A_1	+	+	−	−	M	T	..	12-1-34
49-3	M		−	A_1	+	+	−	−	M	T	..	12-1-34
49-4	M		−	A_1	+	+	−	+	N	t	..	5-30-39
**20-4*	F	H	..	$[A_1]$	..	[+]	..	..	[MN]	[T]	30	8-24-09
**20-4a*	M	h	−	O	+	+	−	+	MN	t	..	..
50-1	F		..	O	+	+	−	+	N	..	..	8-12-33
50-2	M		..	O	+	+	−	+	N	..	..	10-24-31
**20-5*	F	H	..	..	..	[+]	..	..	..	..	31	10-15-11
**20-5a*	M	h	..	O	+	+	−	+	N	..	..	..
51-1	F	h	−	A_1	+	+	+	+	MN	..	..	1-9-41
**20-6*	F	h	−	A_1	+	+	−	+	N	T	..	1-28-15
**20-6a*	M	h	−	A_1	+	+	+	+	MN	..	..	..
52-1	M		−	O	+	+	−	+	MN	..	..	2-27-43
**20-7*	M	H	−	O	+	+	−	+	MN	t	23–25	11-18-18
**20-7*	F	h	−	O	+	+	−	+	MN	..	..	..
53-1	F	h	+	O	+	+	−	+	M	..	..	4-2-41
53-2	M	h	−	A_2	+	+	−	+	M	..	..	1-19-43
**21-1*	F	h	+	O	+	+	−	−	M	T	..	9-2-10
**21-1a*	M	h	−	A_2	−	−	−	+	MN	T	..	..
54-1	F	h	−	A_1	+	+	−	−	M	..	..	10-11-39
54-2	M	h	−	A_1	+	+	−	+	M	..	..	2-8-41
**21-3*	M	h	+	A_1	+	+	−	−	N	T	..	2-10-15
55-3	M	h	+	O	+	−	−	+	N	..	..	6-18-45
**22-1*	M	h	+	O	+	+	−	+	MN	T	..	..
**22-1a*	F	h	−	A_2	−	−	−	+	MN	..	..	..

TABLE 2—*Concluded*

1	2	3	4	5	6	7	8	9	10	11	12	13
56-1	F		+	A_1	+	+	−	+	MN	..	..	9-2-40
56-2	M		−	A_2	+	+	+	+	MN	..	..	12-23-41
**23-1*	F		−	O	+	+	−	−	MN	T	..	8-17-19
**23-1a*	M	h	+	A_1	+	−	+	+	MN	T	..	..
57-1	M		+	O	+	+	−	−	MN	..	..	4-10-43
57-2	M		+	O	+	+	−	−	N	..	..	9-1-45
**23-2*	F	H	+	O	+	+	−	−	MN	T	25	7-22-21
**23-2a*	M	h	−	O	+	+	+	+	N	T	..	..
59-1	F	h	−	A_2	+	+	−	−	N	t	..	5-19-33
59-2	M	h	−	A_1	+	+	−	−	MN	T	..	1-24-35
59-3	M	h	−	A_1	+	+	−	−	N	..	..	7-16-39
59-4	M	h	−	A_1	+	+	−	+	N	..	..	2-16-43
**25-1*	F	h	−	A_1	+	+	−	+	N	T	..	9-3-13
**25-1a*	M	h	−	O	+	+	−	−	MN	T	..	..
61-1	M	h	−	A_1	−	−	−	+	N	..	..	1-14-41
61-2	M	h	−	A_1	−	−	−	+	MN	..	..	7-29-38
**25-3*	F	h	−	A_1	−	−	−	+	N	T	..	11-18-17
25-3a	M	h	−	A_2B	−	−	−	+	MN	..	..	..
62-1	F		−	A_2	+	+	+	+	N	T	..	4-2-39
**25-4*	F	H	..	..	..	..	..	..	..	[T]	19	6-30-19
**25-4a*	M	h	−	A_1	+	+	+	+	MN	t	..	..
63-1	F		−	A_2	+	+	−	+	MN	..	..	4-26-45
**27-1*	F		−	A_2	+	+	−	−	MN	T	..	8-7-25
**27-1a*	M	h	−	O	+	−	+	+	MN	..	..	..

Comment. The method of ascertaining linkage described here is sufficient to indicate that no tight linkage relationships exist between any of the known factors tested. Methods might be employed based on sibships alone without knowledge of either parental genotype, but in the absence of a suggested tight linkage one might record a given sibship in the wrong phase, and the results would then be erroneous. A more accurate method would be to obtain the probable parental genotype in cases where it is unknown, by observing the genotype of siblings, their children, and their parents. As was true with partial sex-linkage, the determination of these suggested linkage relationships and their application awaits the time when many of the members of generation *V* reach or pass the age of onset.[6] Table 2 is included for those investigators

[6] It is the plan of the author to publish subsequent material on this kindred in the *Journal*, as soon as it becomes available. Recently a 45-minute, narrated, technicolor film entitled "Hereditary Ataxia" (PMF 5140), depicting neurologic examinations of *25-2*, *13-3*, *17-2*, *17-5*, *20-2* and *20-7*, has been released by the Army Medical Illustration Service and is available to medical and allied scientists on application to the Signal Corps Photographic Center, 35-11 35th Ave., Long Island City, N. Y.

who are interested in working out suitable methods for utilizing all the available material.

SUMMARY AND CONCLUSIONS

Some clinical, pathologic, and genetic data are recorded for a large American kindred displaying hereditary ataxia. The disease appeared as a dominant trait in 45 members. There was a suggestion that the disease was determined by a partially sex-linked gene, but conclusive evidence for this type of inheritance must await the time when certain members reach the upper limit of the age of onset.

Complete penetrance of the gene was apparent. The age of onset was recorded in 32 instances of the ataxia, usually within a range of years. With one exception, the disease made its appearance before the age of 35, with an overall average of 26.5 years. There exist 51 individuals in the fourth, fifth and sixth generations who by virtue of their parentage may yet exhibit ataxia before the age of 35 years.

An attempt to demonstrate autosomal linkage between five definitely inherited factors and the gene determining the ataxia failed to uncover conclusive evidence for this phenomenon. However, it is possible that a more efficient use of the data may increase certain suggested linkage relationships; therefore the information on these five inherited factors is recorded for use by the interested reader.

ACKNOWLEDGMENTS

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REFERENCES

BELL, J., & CARMICHAEL, E. A. 1938. Hereditary ataxia and spastic paraplegia. *Treasury of Human Inheritance*, Cambridge University Press, Vol. 4, Part 3.

BRAIN, W. R. 1925. The mode of inheritance of hereditary ataxia. *Q. J. Med.*, Oxf. 18: 351–358.

BROWN, S. 1892. On hereditary ataxy, with a series of twenty-one cases. *Brain*, Lond. 15: 250–282.

COOMBS, R. R. A., MOURANT, A. E., & RACE, R. R. 1946. In vivo iso-sensitization of red cells in babies with haemolytic disease. *Lancet*, Lond. 1: 264–266.

COTTERMAN, C. W., & FALLS, H. F. 1944. Genetic studies on ectopia lentis. II. Anthropometric and linkage data. *Ann. Eugen.*, Cambr. 12: 158–168.

GRAY, R. C., & OLIVER. C. P. 1941. Marie's hereditary cerebellar ataxia (olivopontocerebellar atrophy). *Minnesota M.* 24: 327–335.

HALDANE, J. B. S. 1941*a*. The partial sex-linkage of recessive spastic paraplegia. *J. Genet.*, Cambr. 41: 141–148.

HALDANE, J. B. S. 1941*b*. The relative importance of principal and modifying genes in determining some human diseases. *J. Genet.*, Cambr. 41: 149–157.

LEERS, H., & SCHOLZ, E. 1939. Korrelations-pathologische Untersuchungen. Die erbliche Ataxie. *Zschr. menschl. Vererb.* 22: 703–733.

LEVINE, P., BACKER, M., WIGOD, M., & PONDER, R. 1949. A new human hereditary blood property (Cellano) present in 99.8% of all bloods. *Science*, 109: 464–466.

NORTON, H. W. 1949. Estimation of linkage in Rucker's pedigree of nystagmus and color-blindness. *Am. J. Human Genet.* 1: 55–65.

POPENOE, P., & BROUSSEAU, K. 1932. Hereditary ataxia. *J. Hered.* 23: 277–281.

SANGER, R., BERTINSHAW, D., LAWLER, S. D., & RACE, R. R. 1949. Les groupes sanguins humains Kell; fréquences géniques et recherches génétiques. *Rev. hémat.* 4: 32–35.

SCHUT, J. W. 1950. Hereditary ataxia; clinical study through six generations. *Arch. Neur. Psychiat.*, 63: 535–568.

SCHUT, J. W., & HAYMAKER, W. 1951. Hereditary ataxia; pathologic study of five cases of common ancestry. *J. Neuropath. & Clin. Neur.* 1: 183–213.

SJÖGREN, T. 1943. Klinische und erbbiologische Untersuchungen über die Heredoataxien. *Acta psychiat. neur.*, Kbh. Suppl. 24–27: 1–200.

TRIEBEL, H. 1922. Die Familie K., eine Studie über die Vererbung der Friedreich'schen Krankheit (hereditären Ataxie). *Deut. Zschr. Nervenh.* 75: 111–124.

WIENER, A. S., & SONN-GORDON, E. B. 1947. Réaction transfusionnelle hémolytique intragroups due à un hémagglutinogène jusqu'ici non décrit. *Rev. hémat.* 2: 3–10.

Studies in Disorders of Muscle

V. The Inheritance of Childhood Progressive Muscular Dystrophy in 33 Kindreds

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THE cases of muscular dystrophy which have been studied in our laboratory fall with rare exceptions into two types, childhood and facioscapulohumeral progressive muscular dystrophy (Tyler & Wintrobe, 1950). The facioscapulohumeral type, a dominant form of dystrophy, has been described as it occurs in one large kindred (Tyler & Stephens, 1950). This report is concerned primarily with the inheritance of the childhood type in 33 kindreds. A more detailed description of the clinical manifestations of the disease is being presented separately (Tyler & Stephens, 1951) but a brief summary is included here.

METHODS

The data have been collected over a period of many years. By interviews with patients and members of their families (particularly parents) extensive pedigrees have been established for most of the families. All of the patients as well as any of their relatives who gave any indications of having the trait were interviewed and were given physical examinations. In addition, many of the normal sibs have been examined. This did not disclose additional cases. Many of the cases were initially examined by the late Dr. S. C. Baldwin. Many of them have been carefully studied in the Metabolic Ward of the Salt Lake County Hospital. The majority of the patients reported here were residents of Utah. A few have come here for examination and study from other states.

REVIEW OF LITERATURE

Since comprehensive reviews of the literature are available elsewhere, only a very brief review will be presented here. Many reports in the literature are confusing in their descriptions of the disease. It becomes obvious that several different disease processes and different kinds of inheritance are involved in the various kindreds that have been reported.

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Gowers (1879) pointed out that pseudohypertrophic muscular dystrophy in boys was transmitted through normal mothers, especially if it began early in life. When it began later in life it was sometimes transmitted by both males and females. These patients whose disorder began late in life belonged undoubtedly to the facioscapulohumeral or some other type of dystrophy. Polacheck (1941), Arbuse and Sloane (1937), Voshell (1933), Kostakow (1934) and others have presented pedigrees consistent with sex-linked recessive inheritance.

Julia Bell, in a notable work (1943), attempted to take from the literature up to 1943 all of the descriptions of muscular dystrophies. She separated them into several groups on the basis of the symptoms and findings presented. Such a work must, by its nature, share the same inaccuracies of diagnosis and case findings as the original reports. Her hypothesis that all types of muscular dystrophy are caused by the same main gene and that differentiation is due to different modifying factors finds little evidence for its support in our studies.

DESCRIPTION OF THE DISEASE

The birth and neonatal period of the children (all boys) showing childhood progressive muscular dystrophy was consistently uneventful. The first difficulties usually appeared in the third year of life and consisted of a waddling gait, frequent falling and difficulty in running. All of these resulted primarily from involvement of pelvic girdle musculature. In a few cases some delay in beginning to walk was observed. Others had no apparent difficulty until 6 or 7 years of age. In evaluating these statements, however, it should be pointed out that the families in which more than one child was affected dated the onset of the initial difficulty earlier in the second afflicted child. The more carefully observed children were the ones in whom the first definite changes were noted in the first years of life.

As the trait became well established, a characteristic pattern of muscular atrophy and weakness became apparent. This proved to be the best diagnostic criterion of the disorder. The involvement was nearly always symmetrical. The most diagnostically helpful findings were in the pectoralis major and the trapezius muscles, where the early atrophy which occurred in the lower parts of these muscles was quite unlike the atrophy seen in other types of neuromuscular disease.

Pseudohypertrophy of muscle is a curious phenomenon which occurred in the majority of these patients (Tyler, 1950). It consists of enlargement of muscles which are at the same time weak. Pathologically such muscles show marked infiltration by fat and fibrous tissue. The enlargement usually persisted throughout life and was localized in certain pairs of muscles, most frequently the calf muscles, triceps brachii, deltoids and glutei, although nearly any muscle may be involved. Enlargement of the calf muscles was sometimes the

first observed abnormality. It was noteworthy that, even when pseudohypertrophy was found, adjacent groups of muscles showed only atrophy and weakness. The term pseudohypertrophic progressive muscular dystrophy has been used frequently to describe this group of cases but, for reasons outlined elsewhere (Tyler & Wintrobe, 1950), it is better referred to as the childhood type of progressive muscular dystrophy.

The disorder progressed insidiously and slowly so that the majority of children were bed and wheel-chair invalids at 9 to 12 years of age. Death most frequently resulted from intercurrent respiratory infections in adolescence or early adult life.

A few of these dystrophic boys had other congenital abnormalities such as congenital heart disease, arachnodactyly, and coloboma of the iris. The changes which have been observed in the skin, subcutaneous tissues and bone have led to the suggestion that this is a generalized disease of the supporting tissues of the body rather than one affecting muscle only. Consequently, the abbreviated designation "childhood dystrophy" may be used not only as a convenience but as a reminder of the more generalized character of the disorder.

In an occasional patient, myocardial involvement occurred with obscure congestive heart failure. No impairment of the mental faculties was observed. The syndrome is a highly specific one clinically and should not be confused with other neuromuscular disorders.

INHERITANCE

Our conclusions concerning the nature of the inheritance of childhood dystrophy are based on the appearance of the abnormality in 33 separate kindreds. The collection of so many pedigrees showing the same trait in a given geographical area gives an unusual opportunity to study an apparently sex-linked recessive trait as it occurs in a given section of the population. A total of 1,977 normal and 63 dystrophic individuals are presented. From 1 to 10 affected individuals were found in each kindred. The disease was manifest only in the males. Where there was evidence of it passing from generation to generation, it was invariably transmitted through the normal female line. When we examined the kindreds for some pattern of inheritance we found a condition consistent with sex-linked recessive inheritance. Since, however, none of the affected males in any of the 33 kindreds have had any offspring, we were unable to determine whether or not the affected males were able to transmit the trait to their sons. Lack of such critical evidence means that we cannot exclude the possibility of an autosomal gene invariably producing the disease in heterozygous males but not in heterozygous females. When we assume, therefore, that childhood dystrophy is inherited as a sex-linked recessive it is with this one reservation in mind.

Kindreds 64 and 132 might seem to be exceptions to the sex-linked recessive

hypothesis since *II-4* and *II-8*, the great-grandfathers of *V-14* and *V-17*, were brothers. If the trait had been transmitted by these two brothers it would have to be considered as an autosomal recessive rather than as a sex-linked recessive. It would then have to be assumed that the fathers of the two affected sons and their wives were heterozygous for the trait. There was no indication of inbreeding which might tend to bring out a rare autosomal recessive trait. Considering the other kindreds, it seems more likely that two carrier females (*IV-3* and *IV-27*) married by chance into the same large kindred and that each had a dystrophic son.

For convenience in discussion, the kindreds were divided into 3 groups. Group I contained those kindreds (fig. 1) where the trait seemed to be passed down through a line of female carriers from the first known female in the kindred to the affected individuals. Group II contained those kindreds (figs. 2A, 2B) where there were insufficient numbers of males in the direct line from the first known female to the affected individuals to determine whether or not the gene was being transmitted from the first known female. Group III was made up of those kindreds (figs. 3A, 3B, 3C) where there were sufficient unaffected males in a direct line from the first known female to the affected males to make it unlikely that the defective gene had been transmitted through the female line from the first known female in the kindred. This grouping was only made for convenience. It was realized that mutations might have occurred at various places in different pedigrees.

If childhood dystrophy were inherited as a sex-linked recessive in all of these kindreds, approximately one-half of the sons of the theoretical carriers should show the trait. Since, however, many of these females could not be detected because many of them would only be potential carriers the 1:1 ratio would only be approximate. There was a close approximation to the 1:1 ratio in Group I. In Group II, however, most the kindreds have but one affected individual in the pedigree and there were insufficient numbers of males in a direct line from the first known female to give a satisfactory ratio. Kindred 89 is an interesting example. The ancestress *I-1* in this kindred was reared in an orphan asylum and knew nothing about her family. She had but one son and he was affected with childhood muscular dystrophy. This provides little information on which any definite conclusions can be drawn regarding the inheritance of the trait. This and other kindreds in this group might fall into Group I or Group III if more data were available.

Group III is of special interest because of the excessive numbers of normal males in comparison with the defective ones. Although it appears from Group I that the trait is consistent with the sex-linked recessive hypothesis, in Group III there is strong evidence that the trait was not transmitted through the kindreds via a series of female carriers from the first known female in the kindred. What, then, is the explanation? It could be suggested that the clinical

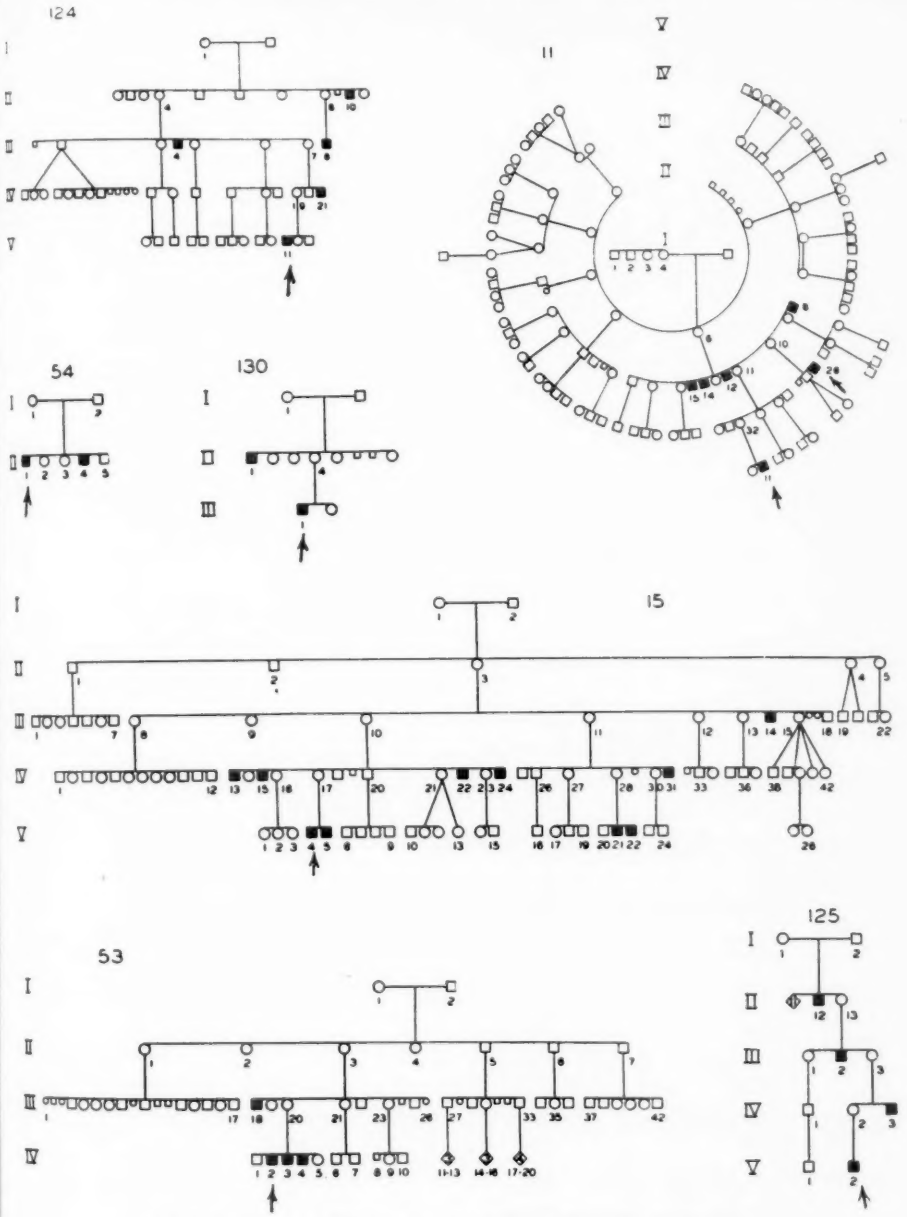

FIG. 1. Pedigrees of Childhood Progressive Muscular Dystrophy, Group I.

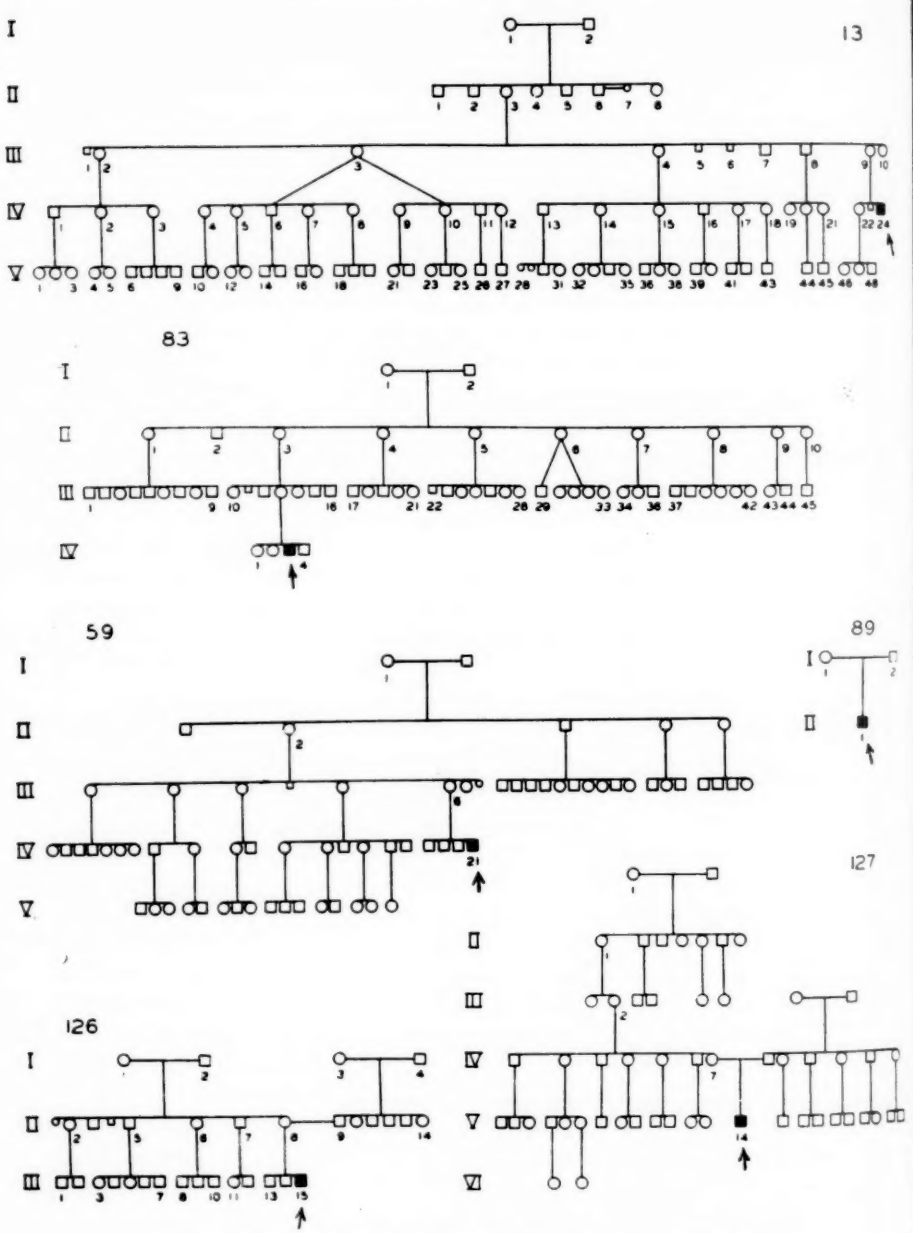

FIG. 2A. Pedigrees of Childhood Progressive Muscular Dystrophy, Group II.

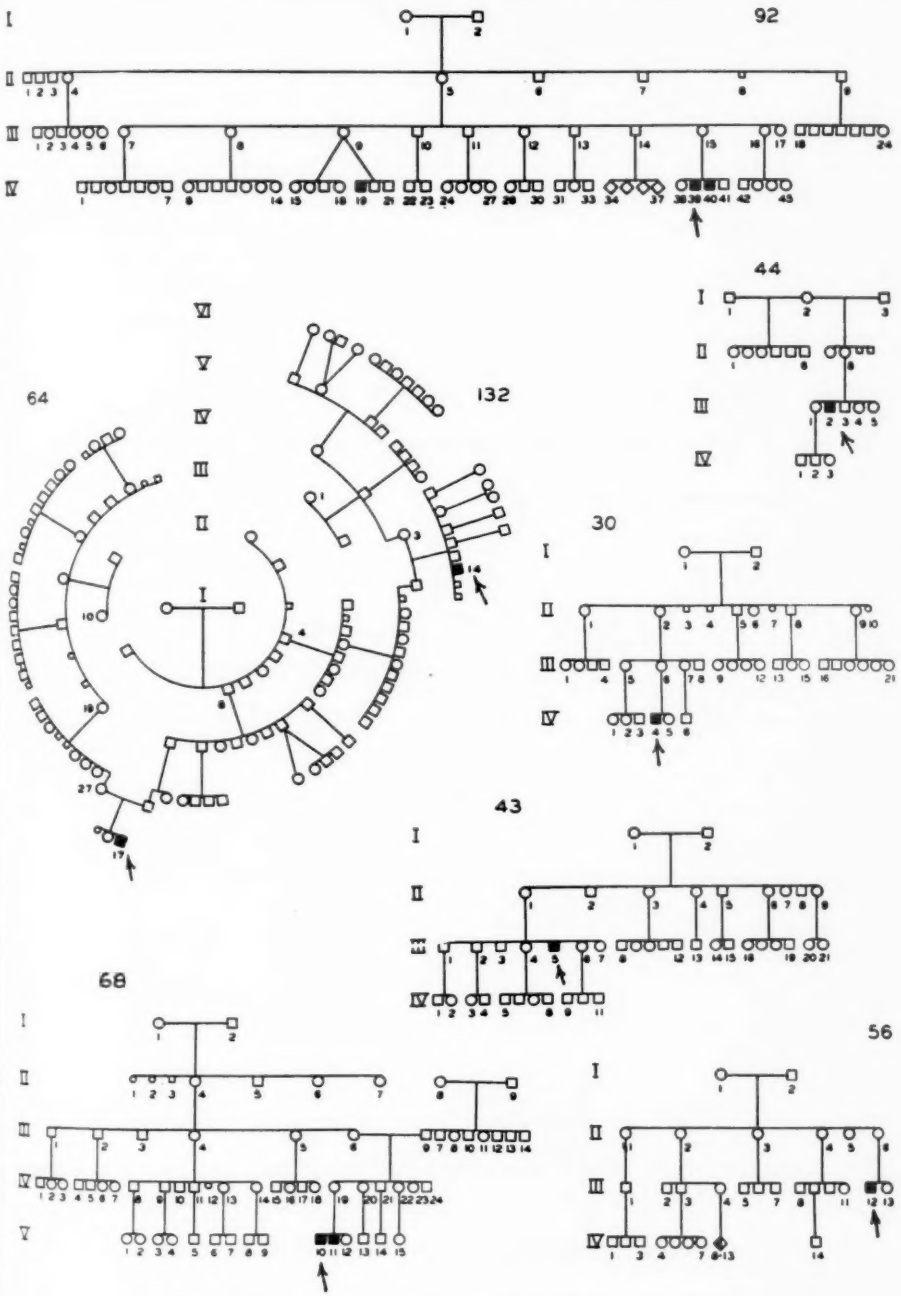

FIG. 2B. Pedigrees of Childhood Progressive Muscular Dystrophy, Group II.

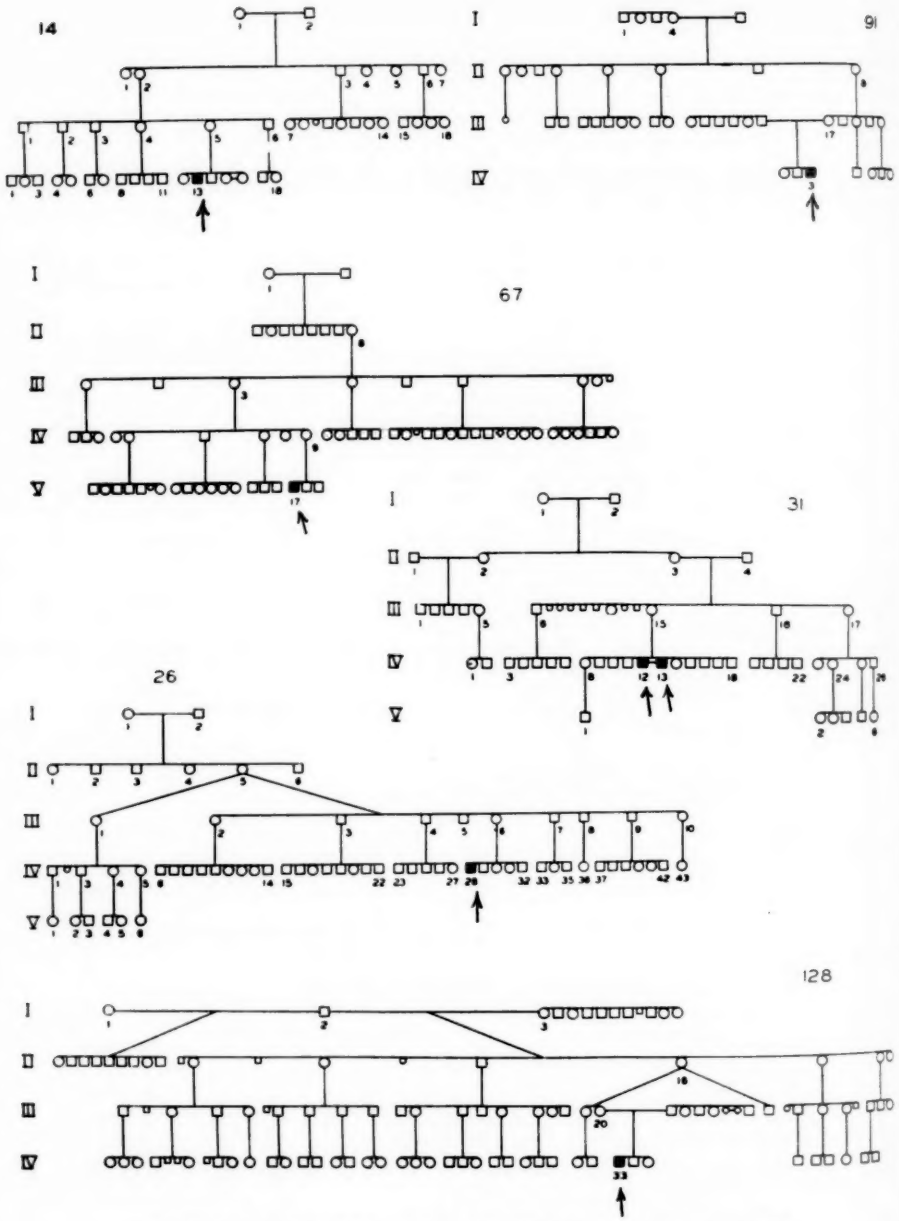

FIG. 3A. Pedigrees of Childhood Progressive Muscular Dystrophy, Group III.

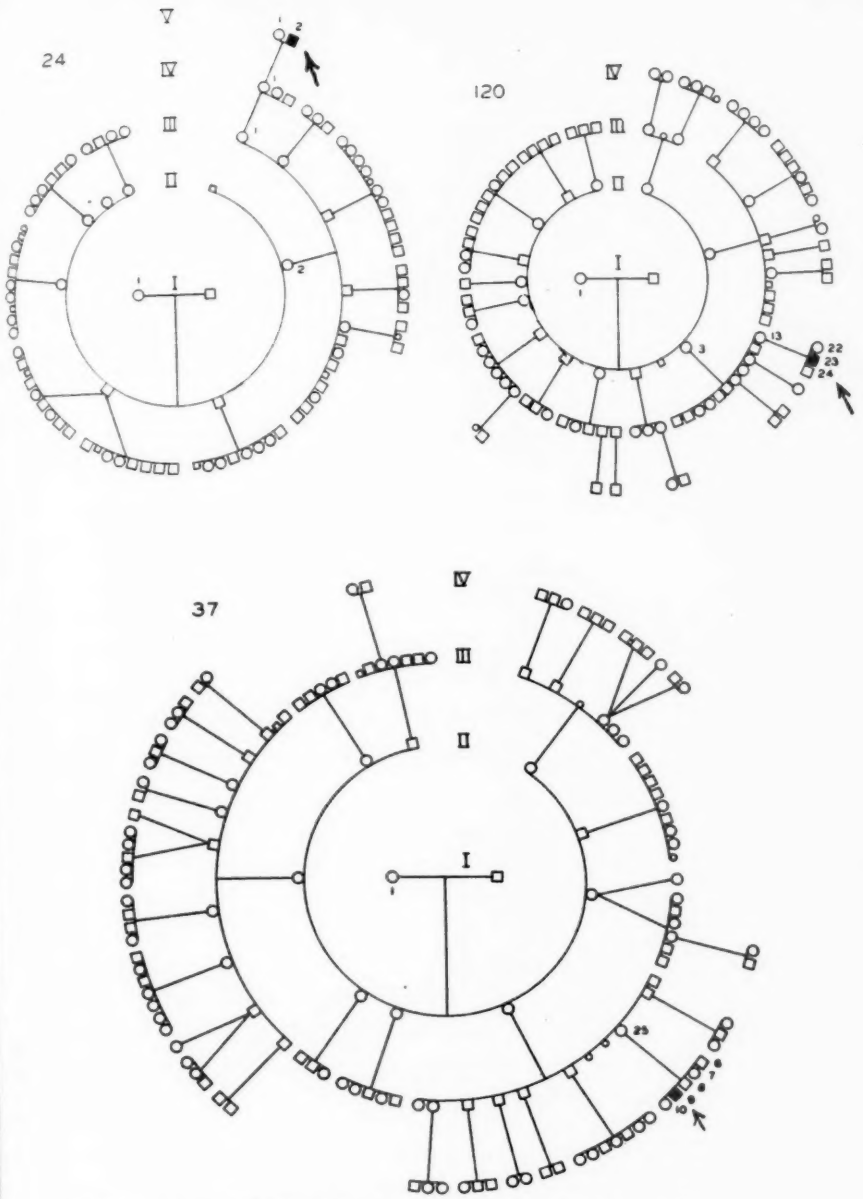

FIG. 3B. Pedigrees of Childhood Progressive Muscular Dystrophy, Group III.

manifestations might be caused by some unknown environmental condition. Since evidence of inheritance of the same trait in Group I is so definite, however, one hesitates to accept this explanation without exploring other possibilities. The other obvious explanation would be that these apparently isolated cases result from recent mutations. Several lines of evidence tend to confirm this hypothesis.

Identical Twins. One of the kindreds is of special interest (see Kindred 31 in table 1 and in fig. 3A, Group III). A pair of identical twins, both of whom

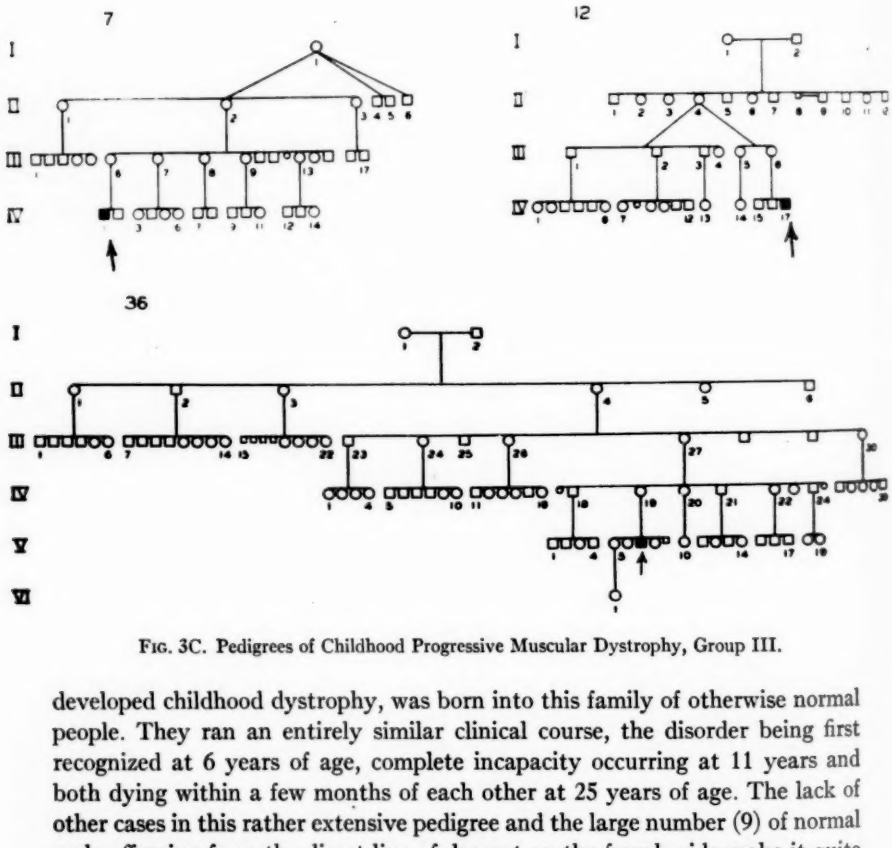

FIG. 3C. Pedigrees of Childhood Progressive Muscular Dystrophy, Group III.

developed childhood dystrophy, was born into this family of otherwise normal people. They ran an entirely similar clinical course, the disorder being first recognized at 6 years of age, complete incapacity occurring at 11 years and both dying within a few months of each other at 25 years of age. The lack of other cases in this rather extensive pedigree and the large number (9) of normal male offspring from the direct line of descent on the female side make it quite improbable that the gene had been present previously, yet the occurrence of the disorder in both twins together with the genetic pattern for the same trait in other kindreds strongly suggests a genetic origin. It seems likely, therefore, that this is a new mutation. The fact that these and all other cases of the disease occur in males further suggests sex-linked recessive inheritance.

Mutation Rate. If childhood dystrophy is always due to a sex-linked recessive gene and occurs only in males who never reproduce, the gene should rapidly disappear from the population if there were no new mutations. Complete data on the frequency of the disease in Utah are not available at the present time. However, all available information has been collected on these cases for many years. It is felt that most of them, especially those born in recent years, are on record although a few cases may have been missed. An enumeration of the affected individuals born in Utah during the period 1931–1941 shows no indication of any decrease in the frequency of childhood dystrophy (table 2). If we conclude on the basis of this evidence that there is no decrease in the frequency of this trait, a high mutation rate must be postulated to replenish the supply of genes depleted through the failure of affected males to reproduce. Not one affected male in any of the 33 kindreds studied has produced any offspring.

If we now take the number of cases in Group III (presumably new mutations) born during the 10 year period, 1931 through 1940, and compare this with the total number of children born in the state during this same period, a "direct" estimate of the minimum mutation rate of the gene for childhood dystrophy is obtained. This period of time was chosen because it was thought that the data would be most accurate. Some affected individuals born before this period may have died without having been examined or reported, while some born after this period may not have been identified as yet. Six of the affected individuals in Group III were born in Utah during this period.

The reports of the state office of vital statistics show that approximately 126,000 children were born in Utah during this same time. If we assume that one-half of these were males, the total group would represent 189,000 X-chromosomes, since each female has two X-chromosomes and each male one. Six mutations would represent the mutations in $\frac{1}{3}$ of these chromosomes; therefore, 6/63,000 should give the approximate mutation rate, or 9.5×10^{-5}. Any cases which might have been missed or may have occurred in Group II would only slightly increase this minimum mutation rate. Since it is seldom possible to calculate a mutation rate by this direct approach, Haldane (1935) following the same line of reasoning, proposed the following formula for calculating the mutation rates of sex-linked recessive traits: $u = \frac{1}{3}(1 - f)x$, where u is the mutation rate, f is the relative fertility of affected males and x is the frequency of the trait among males. Since the total number of affected boys born in Utah during the same interval, 1931–1941, happens to be exactly three times the number of mutations found in the direct method above, the results are exactly the same, e.g. $u = \frac{1}{3} \times 18/63{,}000 = 9.5 \times 10^{-5}$. This mutation rate estimate is one of the highest reported in human genetics. A comparison is shown in table 3.

If the disease is inherited not as a sex-linked receissive trait, but as an autosomal trait appearing in heterozygous males but not in heterozygous females, the mutation rate required for equilibrium would be only half as great, since

TABLE 1. SUMMARY OF DATA BEARING ON AGE AT ONSET AND DURATION OF ILLNESS

GROUP I

KINDRED	PEDIGREE NUMBER	AGE AT ONSET	DATE OF BIRTH	DATE OF DEATH	AGE AT DEATH	AGE IF LIVING
11	*III-8*	—	1895	1910	15	—
	III-12	2	1903	1918	15	—
	III-14	2	1907	1922	15	—
	III-15	2	1911	1928	17	—
	IV-26	7	1920	1937	17	—
	V-11	2	1946	—	—	4
15	*III-14*	—	1893	1911	18	—
	IV-13	—	1904	1927	23	—
	IV-15	—	1908	1924	16	—
	IV-22	—	1922	1938	16	—
	IV-24	—	1926	1939	13	—
	IV-31	—	1923	1940	17	—
	V-4	6	1936	—	—	14
	V-5	5	1939	—	—	11
	V-21	2	1934	—	—	16
	V-22	3	1939	—	—	11
53	*III-18*	—	1900	1922	22	—
	IV-2	6	1928	—	—	22
	IV-3	6	1929	—	—	21
	IV-4	5	1930	—	—	20
54	*II-1*	—	1920	1936	16	—
	II-4	—	1933	—	—	—
124	*II-10*	—	1860	1876	16	—
	III-4	3	1879	1897	18	—
	III-8	5	—	—	—	
	IV-21	8	1923	1940	17	—
	V-11	2	1942	—	—	8
125	*II-12*	—	—	—	21	—
	III-2	—	1894	1910	16	—
	IV-3	2	1930	1950	20	—
	V-2	—	1944	—	—	6
130	*II-1*	—	—	—	13	—
	III-1	3	1943	—	—	7

GROUP II

13	*IV-24*	1	1931	—	—	19
30	*IV-4*	2	1937	—	—	13
43	*III-5*	8	1921	—	—	29
44	*III-2*	9	1923	1943	20	—
56	*III-12*	2	1928	—	—	22
59	*IV-21*	3	1934	—	—	16
64	*V-17*	5	1929	1944	15	—

TABLE 1.—*Continued*

GROUP II.—*Continued*

KINDRED	PEDIGREE NUMBER	AGE AT ONSET	DATE OF BIRTH	DATE OF DEATH	AGE AT DEATH	AGE IF LIVING
68	*V-10*	2	1937	—	—	13
	V-11	2	1940	—	—	10
83	*IV-3*	2	1936	—	—	14
89	*II-1*	4	1938	—	—	12
92	*IV-19*	7	1934	—	—	16
	IV-39	6	1935	—	—	15
	IV-40	7	1940	—	—	10
126	*III-15*	3	1941	—	—	9
127	*V-14*	—	1941	—	—	9
132	*V-14*	—	1922	—	—	28
			GROUP III			
7	*IV-1*	1	1927	—	—	23
12	*IV-17*	2	1936	—	—	14
14	*IV-13*	2	1936	—	—	14
24	*V-2*	2	1928	—	—	22
26	*IV-28*	2	1933	—	—	17
31	*IV-12*	6	1919	1944	25	—
	IV-13	6	1919	1944	25	—
36	*V-7*	5	1930	—	—	20
37	*IV-21*	3	1940	—	—	10
67	*V-17*	3	1932	1948	16	—
91	*IV-3*	2	1927	—	—	23
120	*IV-23*	2	1941	—	—	9
128	*IV-33*	3	1938	—	—	12

there would be 126,000 autosomes represented in the calculation instead of the 63,000 male X-chromosomes.

Size of Families. Because of the early expression and the severe nature of childhood dystrophy it might be thought that the abnormal gene would in some cases be effective before birth or soon after, causing abortions, stillbirths, or an increase in the number of males dying in infancy. There was no obvious evidence that such early deaths were any more frequent in families where dystrophy occurred than in other families belonging to the same kindreds. It would seem probable that the defective gene does not produce clinical manifestations until after the first two or three years of life.

When the mean size of sibships containing cases of dystrophy was compared with that of other sibships in the same kindreds and in the same generations, the former was found to be larger. The average number of children in sibships showing dystrophy was 4.2 as compared with 3.2 in the non-dystrophic sibships in the same generations. This probably can be explained on the basis of ascertainment, i.e., the dystrophic sibships were selected because they contained at least one dystrophic male. The data, however, deserve further examination inasmuch as any real increase in the fertility of heterozygous women would

TABLE 2. NUMBER OF DYSTROPHICS BORN IN A TEN-YEAR PERIOD (1931–1941) IN UTAH

YEAR	NUMBER OF DYSTROPHICS
1931	1
1932	1
1933	2
1934	2
1935	0
1936	4
1937	2
1938	2
1939	2
1940	2
Total	18

TABLE 3. RATES OF MUTATION OF HUMAN GENES (ADAPTED FROM HALDANE, 1949)

GENE	MUTATION RATE	
Chondrodystrophy	4×10^{-5}	(Mørch, 1941)
Hemophilia	3×10^{-5}	(Haldane, 1939, 1947)
Retinoblastoma	1.4×10^{-5}	(Philip & Sorsby, quoted by Haldane)
Aniridia	1.2×10^{-5}	(Møllenback, 1947)
Epiloia	4 to 8×10^{-6}	(Gunther & Penrose, 1935)
Pelger anomaly of leucocytes	8×10^{-5}	(Pätau & Nachtsheim, 1946)
Thalassemia	4×10^{-4}	(Neel & Valentine, 1947)
Childhood muscular dystrophy	1×10^{-4}	(Present study)

tend to counterbalance negative selection in males, thus providing an alternative to the high mutation rate postulated.

Eugenic Implications. While childhood dystrophy occurs only in males, two-thirds of all the defective genes which are capable of producing it are in the female population. Since the males never reproduce, the trait must be transmitted only by the carrier females. In kindreds in which the trait is being transmitted as a sex-linked recessive through the female line, half of the sisters of dystrophic boys may be expected to be carriers. If they are carriers, each son they have has a one to one chance of being dystrophic. Each daughter of a carrier female has a one to one probability of being a carrier. Where the affected child himself is a mutant, he should be the only one in his kindred to develop the trait as a result of this mutant gene. In order to be transmitted in a kindred, a mutation must be present in the egg or sperm which goes to produce a female.

SUMMARY AND CONCLUSIONS

1. A study of 33 separate kindreds in which there were 63 cases of childhood dystrophy is reported. The clinical syndrome is described and the nature of its inheritance analyzed.

2. Progressive muscular dystrophy of childhood is an easily recognizable trait which occurs only in males none of whom ever reproduce.

3. In 7 of the 33 kindreds studied the trait is clearly transmitted as a sex-linked recessive with the possible alternative of an autosomal trait occurring in the heterozygous males but not in the heterozygous females. In 14 kindreds there were insufficient data on which to draw definite conclusions regarding its inheritance and in 12 kindreds there was definite evidence that if the trait be due to a sex-linked recessive gene the cases must represent new mutations.

4. On the basis of data covering a 10 year period, the estimated minimum mutation rate for the sex-linked recessive gene is 1×10^{-4}.

5. The high mutation rate and the failure of affected individuals to reproduce accounts for the frequent sporadic occurrences of the disorder.

REFERENCES

ARBUSE, D. I., & SLOANE, D. 1937. Muscular dystrophy; report of a family. *N. York State J. M.* 37: 1111–1118.

BELL, J. 1943. On pseudohypertrophic and allied types of progressive muscular dystrophy. *Treasury of Human Inheritance*, vol. IV. pt. IV. Cambridge University Press.

GOWERS, W. 1879. Pseudohypertrophic muscular paralysis. London: J. & A. Churchill.

HALDANE, J. B. S. 1935. The rate of spontaneous mutation of a human gene. *J. Genet.*, Cambr. 31: 317–326.

HALDANE, J. B. S. 1949. Mutation in man. *Proc. 8th Internat. Congr. Genetics, Hereditas, Suppl. Vol.* 267–273.

KOSTAKOW, S. 1934. Die progressive Muskeldystrophie, ihre Vererbung and Glykokollbehandlung. *Deut. Arch. klin. Med.* 176: 467–474.

POLACHECK, W. S. 1941. Heredity of pseudohypertrophic muscular dystrophy. *Am. J. Dis. Child.* 61: 1251–1253.

TYLER, F. H. 1950. Studies in disorders of muscle. III. "Pseudohypertrophy" of muscle in progressive muscular dystrophy and other neuromuscular disease. *Arch. Neur. Psychiat.*, Chic. 63: 425–432.

TYLER, F. H., & STEPHENS, F. E. 1950. Studies in disorders of muscle. II. Clinical manifestations and inheritance of facioscapulohumeral dystrophy in a large family. *Ann. Int. M.* 32: 640–660.

TYLER, F. H., & STEPHENS, F. E. Studies in disorders of muscle. IV. The clinical manifestations and inheritance of childhood progressive muscular dystrophy. (To be published.)

TYLER, F. H., & WINTROBE, M. M. 1950. Studies in disorders of muscle. I. The problem of progressive muscular dystrophy. *Ann. Int. M.* 32: 72–79.

VOSHELL, A. F. 1933. Progressive pseudohypertrophic muscular dystrophy. *South. M. J.* 26: 156–166.

The High Familial Prevalence of Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syndrome)

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INTRODUCTION

DURING an investigation (1) of neurocirculatory asthenia, anxiety neurosis, or effort syndrome, some patients said that other family members had symptoms or trouble similar to their own. Such statements, plus clinical impressions, suggested that the familial prevalence of this disorder should be especially investigated. This study was planned to achieve the following ends: firstly, to ascertain the frequency of the disorder in parents, brothers, and sisters of patients with the disorder; secondly, to investigate and analyze the pattern of familial prevalence in affected families; thirdly, to determine, if possible, if the disorder were hereditary or acquired, or both; fourthly, to provide a basis for further studies in order to clarify specific detailed problems relating to the familial prevalence of the disorder.

PROCEDURE

The families of 139 patients with neurocirculatory asthenia, 25 convalescent control subjects, and 55 healthy control subjects were investigated. Reliable information as to the occurrence of neurocirculatory asthenia in families was obtained from 67 patients with chronic neurocirculatory asthenia, 44 patients with acute neurocirculatory asthenia, 18 convalescent control subjects, and 54 healthy control subjects. Data were not included when the subject did not remember his mother or father, when the parent died at or before the age of 30, or when, in the opinion of the investigators, general factors of low intelligence, evasiveness or poor or incomplete information made the data so unreliable as to preclude their use.

The interview method was used. The patient was interrogated from a check list which covered 125 points. The portion of that list especially relevant to

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this study was listed as family history and included the following questions: Anyone in the family have nervousness? Anyone in the family faint? Anyone in the family have nervous breakdown? Anyone in the family have heart attacks? Anyone in the family have angina pectoris? Anyone in the family have breathing trouble? Anyone in the family have high blood pressure? Anyone in the family have the same trouble as patient? If any of the above were answered by "yes," further relevant questions were asked, in no set pattern, to amplify and clarify the diagnosis using appropriate clinical methods of history taking. In 15 subjects the relative was examined in order to compare the information and diagnosis gained by direct examination with that of the interview with the index case.

Data were analyzed by means of standard statistical and mathematical genetic methods. These calculations included: *a*) the significance of the difference between proportions and means (2); *b*) the probability of the occurrence of deviations (3); *c*) the comparison of the actual number of affected cases in each position of birth rank in a sibship with the expected number, "long-table" method (4, 5); *d*) the number of contiguous affected cases actually observed compared with the number expected by random distribution (6); *e*) the comparison of the actual number of affected cases in sibships of varying size with the number expected according to standard genetic ratios: simple dominant and recessive (7), double dominant, double recessive and triple dominant (8), and the variance and significance ratios of these (9); *f*) expected proportion of families of index cases with both parents normal, one parent affected and both parents affected for various gene frequencies, recessive and double dominant hypotheses (8). Gene frequencies were calculated for each disease prevalence from general Mendelian principles, assuming non-assortative mating, and for double dominants, assuming equal frequency of both dominant genes (8, 10, 11).

Definitions and Terminology

In this study neurocirculatory asthenia (N.C.A.), anxiety neurosis, neurasthenia and effort syndrome were regarded as synonymous terms representing the same disorder (1, 12). Whether this disorder represents one or several disease entities is not as yet clear; however, these terms as commonly used offered no useful basis for further differentiation. The diagnosis of N.C.A. in an index case was based on its characteristic symptoms (1, 12, 13).

The index case (proband) was the patient with N.C.A. or the control subject whose relatives were investigated for evidence of neurocirculatory asthenia or its absence. The term "patient" refers always to the index case with N.C.A. the term "affected" is used to describe the abnormal relatives or families with affected cases other than the index case. "Affected cases" in a sibship include the index case.

In patients (index cases or probands) a division was made between *chronic* and *acute* neurocirculatory asthenia. This division was made on history alone (12, 14); it was further proved to correspond with quantitative laboratory differences (1, 14, 15, 16), which strengthened the conclusion that the division between acute and chronic N.C.A. was a valid one (1). In brief, those who had a lifelong course of the disorder or who could never do hard work or athletics were designated 'chronic N.C.A.', while those who gave convincing evidence of good health, ability to do muscular work or athletics, and nervous stability previous to the onset of the illness were designated 'acute N.C.A.' The method of separation of the patients into 'acute' and 'chronic' was at best arbitrary and fairly crude, but the decision in any individual case was always made independently of the family history.

Convalescent patients were Army soldiers who had had bone wounds or injuries, had developed osteomyelitis and were under penicillin therapy. They were practically all well enough to be up and about and to go out of the hospital for visits. This group was included in order to learn whether being sick oneself led to describing excess of symptoms in relatives. Three patients in this group also suffered from chronic N.C.A. Their data were retained in the study, however, as this seemed the least confusing way to handle the problem. The decision as to diagnosis in their cases as in all cases in the study was made independently of the family history.

Healthy control subjects were soldiers who were in good state of health, had been through basic training and were not considered medical or disciplinary problems in their units. Two of these subjects were diagnosed N.C.A. but their data were retained with that of the healthy group.

The term "familial prevalence" was defined as referring to occurrence in any close relative, i.e. mothers, fathers, sisters, brothers. In some genetic writings the term "familial" is used to refer to disease occurring in siblings but not in parents (5), and hence it often implies a recessive condition. The term is not used in that restricted sense in this report, however.

Relatives were divided into three groups: 1) neurocirculatory asthenia (N.C.A.), 2) probable N.C.A., 3) no N.C.A. Relatives with characteristic symptoms of N.C.A. were believed definitely to have the disorder and were so diagnosed. Those for whom data were incomplete but suggestive of N.C.A., or for whom an alternate but less likely diagnosis was possible, were called 'probable N.C.A.' Those who had no symptoms or whose symptoms were non-diagnostic were called 'no N.C.A.' Decision as to diagnosis in relatives was originally made on clinical impression, but eventually, in order to use strictly comparable standards in diagnosis in the patient and control groups, a systematic method of diagnosis was evolved based on clinical facts concerning N.C.A. (table 1). This system was adhered to rigidly in the final decision as to diagnosis in the relatives of both patient and control groups. The number of alcoholic

relatives was noted. 'Alcoholic' refers to a person who had difficulties related to the excessive use of alcohol according to the opinion of both the patient and the examiner.

No relatives younger than 18 years of age and none who died before the age of 18 were included in the study, since N.C.A. usually does not develop before that age. This conclusion is based on another study, some of the data of which have already appeared (17), which showed that in 60 well-studied cases

TABLE 1. CRITERIA FOR DIAGNOSIS OF NEUROCIRCULATORY ASTHENIA (ANXIETY NEUROSIS, EFFORT SYNDROME) BASED ON INFORMATION FROM INDEX CASE

I. NERVOUS	II. CARDIOVASCULAR	III. FATIGUE	IV. DIAGNOSES
"Nervous"	Short of breath	Tires easily	Same as patient
Apprehensive	Breathlessness	Can't work	Nervous heart
Fears	Palpitation	Never could do hard work	Tired muscle
Restless	Chest discomfort	Never healthy	Low blood pressure
"Trembly"	Chest pain	Skinny	"Thyroid trouble"
Headaches	Chest pressure	Weak	Nervous breakdown
Insomnia	Dizzy spells	Rests a lot	"Anemia"
Dizzy	Anxiety attacks	Not robust	
Faints		"4-F"	
Faintness			
Dizzy spells			
Anxiety attacks			
Nervous spells			
Irritable			
Rejected by army for nervousness			

Four categories of information from history were set up. Category I consists predominantly of "neuropsychiatric" symptoms; II predominantly of "cardiovascular" symptoms; III of more general symptoms and disability; IV of diagnoses commonly used for the disorder. Minimal diagnostic criteria for neurocirculatory asthenia: Any symptom in I plus any symptom in II; any symptom in II plus any symptom in III; "diagnoses" in IV or "anemia" plus any symptom in I; dizzy spells plus one more symptom. Diagnostic criteria for probable neurocirculatory asthenia: Any symptom in I and any symptom in III; any symptom in II; several symptoms from I; fainting plus any other symptom in a man; "many nervous breakdowns." The diagnosis is based on the presence of complaints of the above symptoms in the absence of any other diagnosis, definite or probable, medical, psychiatric or other, to explain them.

only 20.8% began before 18 and that the mean age of onset was 24.95 years. No parents who died at or before age 30 were included in the study, as the subjects seemed to have but slight knowledge of such parents. 'Family' as used in this study refers to immediate family of the index case, i.e. parents, brothers and sisters only.

In a few families information about relatives other than parents and siblings was obtained, but there was so little reliable or complete information of that sort that it was not deemed usable for this report. 'Relatives' thus refers to either mothers, fathers, brothers or sisters.

Differences between means and proportions which were equal to or greater than twice the standard error of the differences ($t \geq 2$) were called "statistically significant"; the probability of such a deviation occurring by chance is approximately 5 per cent or less ($P \leq 0.05$).

RESULTS

Prevalence of N.C.A. in relatives of patients with chronic N.C.A.

The proportion of fathers with neurocirculatory asthenia (anxiety neurosis, effort syndrome) is higher in the chronic N.C.A. group than in the control groups (fig. 1); this difference, 17.5% *vs.* 0.0% (table 2), is statistically significant ($t = 3.2$, table 3).

The prevalence of N.C.A. in mothers of patients with chronic N.C.A. is 54.8% (table 2); this is in sharp contrast to the percentage of 1.9% and 16.7% in the two control groups and 5.6% in the combined data of both control groups. The difference in proportion of affected mothers between patients and controls is highly significant (chronic *vs.* healthy, $t = 6.2$; chronic *vs.* convalescent, $t = 2.86$). (Cf. table 3). It should be noted (fig. 1) that the 3 cases of N.C.A. in mothers in the convalescent control group were in mothers of control subjects who had been diagnosed as having N.C.A. In families with no affected children only one mother had N.C.A.

It will be noted that there are more affected mothers than fathers, 54.8% *vs.* 17.5%. ($t = 4.35$, highly significant.)

Of 98 brothers of patients with N.C.A., 13.3% had the same diagnosis. This compares with no cases in 83 brothers of the healthy control subjects (significance ratio, $t = 3.33$).

Of 99 sisters of patients with chronic N.C.A., 12.1% are affected, as compared with zero per cent in the healthy control series. This difference (cf. tables 2, 3) is significant ($t = 3.43$).

At least one case of N.C.A. in addition to the index case appeared in the family (parents or siblings) of 67.2% of 58 families of men with chronic N.C.A. When 'probable' cases were included, 74.1% of 58 men with chronic N.C.A. showed at least one affected relative.

These data show that there is a highly significant excess frequency of N.C.A. in parents, siblings and families of patients with chronic N.C.A.

Prevalence of N.C.A. in relatives of patients with acute N.C.A.

There were but few cases of the disorder in relatives of men with acute N.C.A. (fig. 1, table 2): 4 cases in mothers, 4 cases in brothers, and 1 case in a father. There was no significant difference between the control subjects and

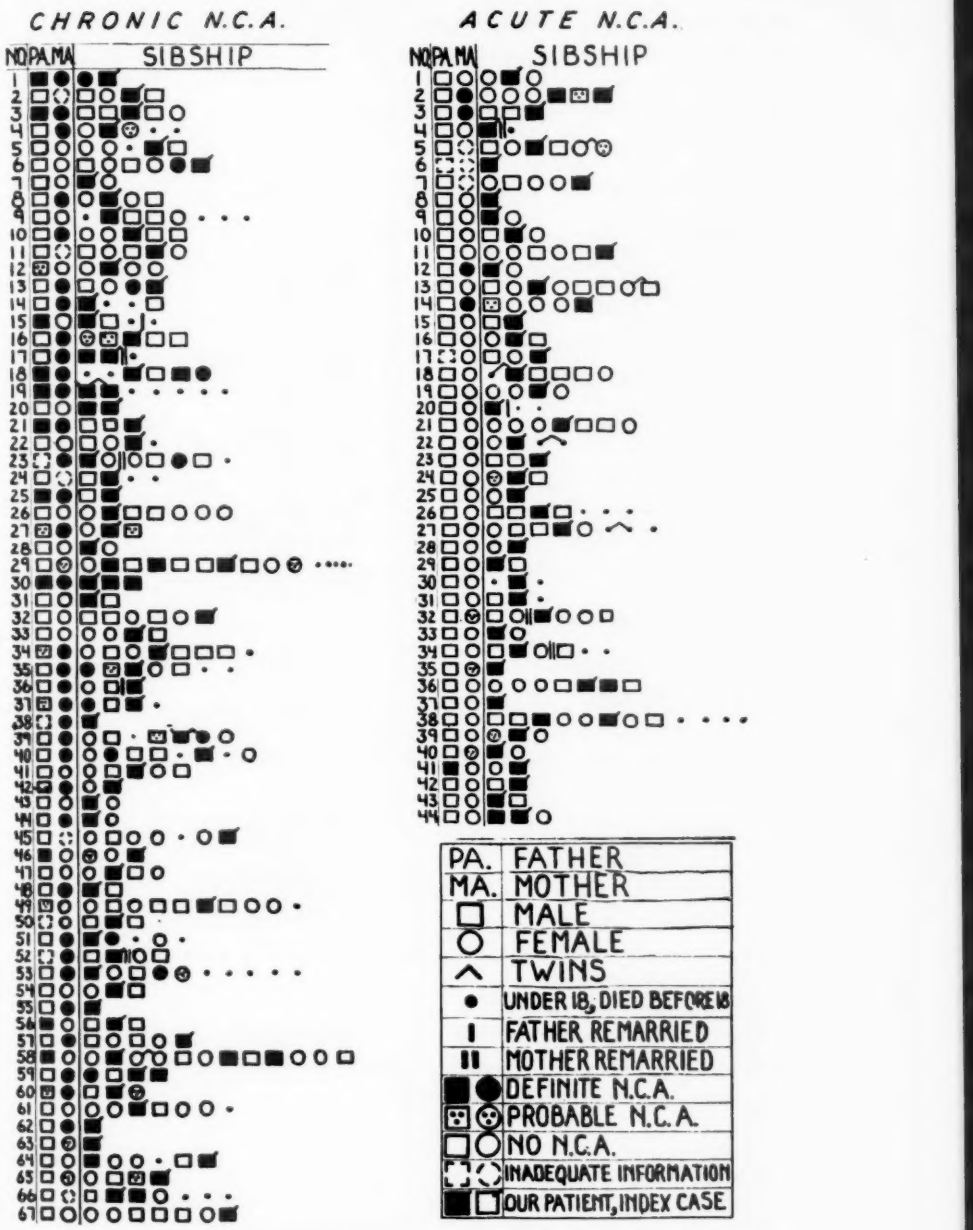

FIG. 1A. Summary of data on neurocirculatory asthenia in the families of 67 chronic N.C.A. patients and 44 acute N.C.A. patients.

acute neurocirculatory asthenia patients with regard to prevalence of N.C.A. among the relatives, except in brothers.

N.C.A. appeared in a member of the family other than the patient in 8 or 20% of the 40 families. This contrasts with 1 case in 1.9% of families of the healthy control subjects ($t = 2.96$).

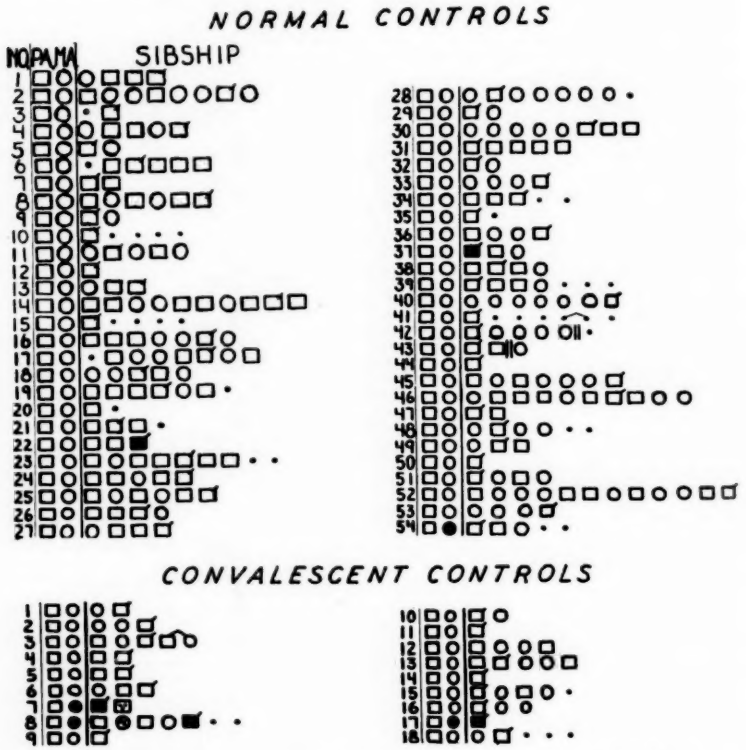

FIG. 1B. Summary of data on neurocirculatory asthenia in the families of 54 healthy controls and 18 convalescent controls.

The data thus suggest a slight, but definite, familial prevalence of N.C.A. in families and brothers of patients with acute N.C.A., if one can assume that not many cases of chronic N.C.A. were erroneously included.

Prevalence of N.C.A. in relatives of patients with chronic N.C.A. and acute N.C.A.

It can be seen from table 2 that, for all classes of relationship, the frequency of N.C.A. is higher in relatives of patients with chronic N.C.A. than in those

with acute N.C.A. The excess is statistically significant in all classes, excepting brothers (table 3).

TABLE 2. FREQUENCIES OF NEUROCIRCULATORY ASTHENIA (ANXIETY NEUROSIS, EFFORT SYNDROME) IN RELATIVES OF PATIENTS WITH N.C.A. AND OF CONTROL SUBJECTS

SOURCE OF INDEX CASE	67 PATIENTS WITH CHRONIC N.C.A.			44 PATIENTS WITH ACUTE N.C.A.			18 CONVALESCENT CONTROL SUBJECTS			54 HEALTHY CONTROL SUBJECTS		
Family member or family group in tabulation	Total no.	Affected		Total no.	Affected		Total no.	Affected		Total no.	Affected	
		No.	%		No.	%		No.	%		No.	%
Fathers	63	11	17.5	42	1	2.4	18	0	0	54	0	0
Mothers	62	34	54.8	41	4	9.8	18	3	16.7	54	1	1.9
Sibs	264	92	34.8	146	48	32.9	48	3	6.3	228	2	0.9
Brothers	98	13	13.3	47	4	8.5	12	0	0	83	0	0
Sisters	99	12	12.1	55	0	0	18	0	0	91	0	0
Families	58	39	67.2	40	8	20.0	18	3	16.7	54	1	1.9
Sibs in families with no affected parents	102	28	27.5	113	38	33.6	40	0	0	225	2	0.9
Sibs in families with 1 affected parent	106	40	37.7	18	6	33.3	8	3	37.5	3	0	0
Sibs in families with both parents affected	21	13	61.9	—	—	—	—	—	—	—	—	—
Mean no. of sibs per family	3.94			3.32			2.67			4.22		
Mean age of index case (yrs.)	27.13			26.86			24.61			24.13		

Only parents and sibs above 18 years of age for whom adequate data on N.C.A. status are available are included in the calculations. Families with one or both parents of unknown status are excluded. "Mean number of sibs per family" includes the index case, plus all known sibs of age 18 years or over. Index cases are also counted in the frequency data for "sibs," but not for "brothers."

TABLE 3. COMPARISON OF PERCENTAGES OF AFFECTED RELATIVES FOR CHRONIC N.C.A. PATIENTS, ACUTE N.C.A. PATIENTS, AND HEALTHY CONTROLS

CLASS OF RELATIVES	PERCENTAGE AFFECTED RELATIVES			*t*-RATIO FOR DIFFERENCES		
	Chronic N.C.A. patients (A)	Acute N.C.A. patients (B)	Healthy controls (C)	A-B	A-C	B-C
Fathers	17.5	2.4	0	2.38*	3.23*	1.14
Mothers	54.8	9.8	1.9	4.64*	6.20*	1.71
Brothers	13.3	8.5	0	0.83	3.33*	2.70*
Sisters	12.1	0	0	2.69*	3.43*	0
Families	67.2	20.0	1.9	4.60*	7.22*	2.96*

* Statistically significant difference.

This demonstrates that more relatives and families are affected in chronic N.C.A. than in the acute form of the disorder, and serves as further evidence for the validity of the separation between the two disease types.

Prevalence of N.C.A. plus 'probable N.C.A.' in relatives of patients with chronic N.C.A.

Tabulations were made (table 4) estimating the prevalence of N.C.A. when 'probable' cases were added to cases of N.C.A. in fathers, mothers, brothers and sisters (table 4-II). There was but little difference in the prevalence of N.C.A. alone and N.C.A. and probable N.C.A. taken together. None of these slight differences was statistically significant. Thus, adding the probable cases into the calculations makes no practical difference in the results.

TABLE 4. 67 FAMILIES OF CHRONIC N.C.A. PATIENTS. FREQUENCIES AMONG RELATIVES OF: (I) NEUROCIRCULATORY ASTHENIA; (II) PROBABLE N.C.A. PLUS N.C.A.; (III) N.C.A. PLUS ALCOHOLISM; (IV) N.C.A. PLUS PROBABLE N.C.A. PLUS ALCOHOLISM

TYPE OF DISORDER TABULATED IN FAMILY MEMBER OR FAMILY GROUP→	I N.C.A.			II N.C.A. PLUS PROBABLE N.C.A.			III N.C.A. PLUS ALCOHOLISM			IV N.C.A. PLUS PROBABLE N.C.A. PLUS ALCOHOLISM		
Family member or family group	Total no.	Affected		Total no.	Affected		Total no.	Affected		Total no.	Affected	
		No.	%		No.	%		No.	%		No.	%
Fathers	63	11	17.5	63	17	27.0	63	22	34.9	63	26	41.3
Mothers	62	34	54.8	62	37	59.7	62	34	54.8	62	37	59.7
Brothers	98	13	13.3	98	18	18.4	98	18	18.4	98	22	22.4
Sisters	99	12	12.1	99	18	18.2	99	12	12.1	99	18	18.2
Families—0 affected parents	58	23	39.7	58	18	31.0	58	16	27.6	58	12	20.7
Families—1 affected parent	58	28	48.3	58	29	50.0	58	31	53.4	58	32	55.2
Families—2 affected parents	58	7	12.0	58	11	19.0	58	11	19.0	58	14	24.1
Sibs in families with 0 affected parents	102	28	27.5	74	21	28.4	67	24	35.8	48	15	31.3
Sibs in families with 1 affected parent	106	40	37.7	118	51	43.2	126	41	32.5	132	52	39.4
Sibs in families with 2 affected parents	21	13	61.9	37	20	54.1	36	21	58.3	49	29	59.2

Mean number of children per family = 3.94.
Mean age of patients (index cases) = 27.21 years.

Observations on convalescent war wound patients

The familial prevalence of N.C.A. for control patients convalescing from osteomyelitis was studied. The purpose was to determine whether sickness, hospitalization and convalescence not due to N.C.A. could so affect a man's attitude or memory that he would describe a high prevalence of N.C.A. or symptoms of the disorder in his relatives. Observations were made on 25 patients. Adequate family data were obtained in 18 of those cases. Three of the control patients in this group were diagnosed N.C.A. This was believed to have existed before the recent illness with, and convalescence from, osteo-

myelitis. It is of interest that the mothers of those 3 men were also affected. For the sake of avoiding one type of complication these cases were all retained in the convalescent group. They furnish further evidence for the familial prevalence of N.C.A. In the other 15 cases, no relatives with N.C.A. were described by the control patients.

It was concluded that symptoms in patients do not necessarily lead the patients to describe more symptoms of neurocirculatory asthenia in relatives than do healthy control subjects.

Prevalence of N.C.A. in all sons and daughters in relation to number of affected parents

In families of cases with chronic N.C.A. where no parents had N.C.A. (table 2) only 27.5% of the children were affected. Since these families averaged 3.94 children, this 27.5% represents little more than the index case; that is, the index case is affected, and, on an average, 3 sibs are not. Actually only 5 of 79 sibs had neurocirculatory asthenia (table 4). This shows that where there are no affected parents, there are almost no affected brothers and sisters. There is slight evidence of a familial tendency in these families.

When 1 parent is affected, 37.7% of the children are affected; when 2 parents are affected, 61.9% of the children are affected. The difference between the prevalence of affected children when both parents are affected is significant both as compared with those families where no parents are affected ($t = 3.05$) and as compared with families where 1 parent is affected ($t = 2.05$). The difference between the prevalence of neurocirculatory asthenia in the children of 1-parent families and no-parent families is not significant ($t = 1.58$).

When index cases are omitted, the proportion of affected sibs ("secondary attack rate") is: for families with no affected parents, 5 out of 79 or 6.33%; for families with 1 affected parent, 12 out of 78 or 15.38%; for families with 2 affected parents, 6 out of 14 cases or 42.86%. The significance ratios between these proportions are: no parent *vs.* 1 parent, $t = 1.82$; no parent *vs.* 2 parents, $t = 3.90$; 1 parent *vs.* 2 parents, $t = 2.39$.

In acute neurocirculatory asthenia, the "secondary attack rate" is 2.7% when no parents are affected, 5.6% when 1 parent is affected.

In the acute N.C.A. patients, 33.6% of children in no-parent families were affected as compared with the almost identical 33.3% in families with 1 affected parent.

There is no striking change in percentage of affected sibs in the no affected parents, 1 affected parent and 2 affected parents groups when 'probable' cases and 'alcoholic' cases are included in the calculations (table 4). The slight differences are not significant ($t = 0.48, 0.26, 0.22$, resp.).

These data show that when 2 parents are affected there are more cases affected in their children than when only 1 parent is affected. When no parent

is affected, neurocirculatory asthenia scarcely appears in the children except in the index case.

Alcoholism in relatives: Observations as to its prevalence and calculations assuming that alcoholic relatives might be cases of N.C.A.

More cases of alcoholism (table 4) appeared in fathers and brothers of patients with chronic N.C.A. than in fathers and brothers of comparable control subjects. There were 12 alcoholic fathers in the 63 fathers of chronic N.C.A. patients and 5 alcoholic brothers among 98 in the chronic N.C.A. group; this contrasted with 2 cases in the 54 fathers of the healthy controls and 1 case in the 83 brothers of healthy controls. This shows that there is significantly more alcoholism in fathers of N.C.A. patients than in fathers of healthy control subjects. When calculations were made assuming that alcoholic fathers and brothers were really cases of neurocirculatory asthenia, this significantly raised the number of affected fathers to 34.9% (table 4—III) a level approaching the ideal 50% demanded by a disorder which was a Mendelian dominant with a single gene involved.

Using this assumption, 35.8% of the children of no affected parents would show N.C.A., 32.5% of 1-affected-parent families and 58.3% of 2-affected-parent families.

These data suggest the possibility that cases labelled "alcoholism" might really be cases of neurocirculatory asthenia (anxiety neurosis, effort syndrome) and that such cases should be studied directly, and in detail, to rule in or out that possibility.

Prevalence of N.C.A. in spouses of affected parents

In families of chronic N.C.A. patients, when both parents are known, 7 of 31 mothers with N.C.A. had affected husbands, i.e., 22.58% (fig. 1). Of 11 fathers with N.C.A., 7 had affected spouses, i.e., 63.64%. This high frequency of the disorder among spouses of affected parents differs significantly from its estimated frequency (13) of 5.6% in the general population. The significance ratio of the difference from the general population incidence is, in wives of affected husbands, $t = 6.87$; in husbands of affected wives, $t = 3.37$. The numbers involved are small for final conclusions.

In families of acute N.C.A. no cases were noted with both parents affected (fig. 1).

Birth order and contiguity of affected individuals within sibships

Sibships were examined to determine: 1) whether there were more affected individuals in any position of birth order in the family than could be explained by random distribution, 2) whether affected sibs occurred *in succession* more often than would be expected by chance.

37.87% of 66 first children were affected; 37.09% of 62 second children; 40.42% of 47 third children; 22.85% of 35 fourth children and 30.43% of 23 fifth children (fig. 1). The percentage of all affected sibs was 34.8%.

Analysis of the data for order of birth of affected members of a sibship was undertaken by means of the long-table method of Pearson (4), as shown in table 5. In this table, all twins are excluded, as well as all sibs who had not reached the age of 18 years. When such sibs were excluded, the next one assumed the position of the excluded sib. This same calculation done with each sib retaining his actual birth position in the table gave approximately the same result and led to the same conclusions.

TABLE 5. ORDER OF BIRTH OF AFFECTED MEMBERS OF THE SIBSHIPS

The table includes the index cases and all affected sibs who lived to the age of 18 years or over. Twins are excluded.

ORDER OF BIRTH, r	SIZE OF SIBSHIP, s										TOTAL NUMBER OBSERVED	TOTAL NUMBER EXPECTED
	1	2	3	4	5	6	7	8	9	10		
1	4	11	3	3	3	1	0	0	0	0	25	27.99
2	—	6	8	5	0	1	1	0	0	2	23	23.98
3	—	—	6	7	5	1	0	0	0	0	19	15.49
4	—	—	—	4	2	0	1	0	0	1	8	9.82
5	—	—	—	—	3	3	0	0	0	1	7	5.07
6	—	—	—	—	—	2	0	0	1	0	3	2.47
7	—	—	—	—	—	—	1	0	0	2	3	1.14
8	—	—	—	—	—	—	—	0	0	0	0	0.71
9	—	—	—	—	—	—	—	—	0	0	0	0.71
10	—	—	—	—	—	—	—	—	—	0	0	0.60

From this analysis it was concluded that order of birth is not a factor in the occurrence of the disorder.

An affected case with chronic N.C.A. is followed immediately by an affected case in 13 of 65 cases, that is 20% of the time, with a standard error of $\pm 4.96\%$. A method of calculation (6) which takes into account family size and the overall proportion of affected cases of 0.348 gives the expected number of contiguous cases as 22.5. This shows that an affected case does not follow immediately another affected case more often than might be expected by chance.

It can be concluded that there is random distribution of affected cases in the fraternities; this is believed by some investigators to be evidence for the hereditary nature of a disease (5).

Comparison of information from histories and from direct examination

In 15 instances, direct examination of the relative was made, in addition to eliciting information about that relative from the patient. In 13 cases, the

presence or absence of neurocirculatory asthenia, as evidenced from the patient's history, was confirmed by direct examination. These data showed that history diagnosis agreed with the examination diagnosis in 87% of these cases when the comparison was made. The histories of 2 relatives suggested that they did not have the disorder; examinations proved that they did have it. These data are obviously insufficient for complete validation of the history method. It is possible even that more data might reveal a consistent error in the direction of too few cases diagnosed by the history method.

It was concluded from these comparisons that although there was good agreement in diagnoses arrived at by history and by direct examination in a few cases, a study with direct examination as in our second study (19) was necessary.

Comparison of results of two diagnostic methods: Clinical method vs. Systematic method

When the usual clinical method was used as a basis of diagnosis of 70 cases of chronic N.C.A., the proportions of diagnoses arrived at were: affected fathers, 20.0%; affected mothers, 45.7%, and affected brothers and sisters, 13.2%. These do not differ materially (significance ratios, respectively: 0.37, 1.05, 0.14) from the proportions arrived at by the method described in table 1 and reported in table 2.

This shows that the results of the systematic method of diagnosis agree with those of the usual clinical method in which the physician arrives at a diagnosis without resort to a systematic tabulation of symptoms.

Testing the data of chronic N.C.A. under various genetic hypotheses

A. Simple Dominance (Single Dominant Gene Substitution)

Affected parents: Table 4 and figure 1 show that 39.7% of the families have no affected parents. There should be no families without affected parents in simple dominant heredity, unless the disorder has "low penetrance" (i.e., some abnormal genotypes are not affected phenotypes).

Affected sibs: When no parents are affected, 27.5% of the sibs are affected; 5 cases in addition to the index cases are affected. For the simple dominant, no cases in children should be affected unless 1 parent is affected. When 1 parent is affected, 37.7% of the sibs are affected; when 2 parents are affected, 61.9% of the children are affected. Although these proportions approximate the ideal proportions of 50% and 75% respectively and show no significant deviation from these proportions (χ^2 = 1.8, 0.91), they do not take into account the families with no affected cases. When adjustments are made (11) for the distribution $p = \frac{1}{2}$, $q = \frac{1}{2}$ (affected 50%, non-affected 50%), the ob-

served number of cases, 40, is significantly lower ($t = 4.1$) than the number demanded by the hypothesis: 58.64 (table 6).

Sex proportions: The number of affected mothers (54.8%) is significantly higher than the number of affected fathers (17.5%). In the simple dominant the proportion of affected mothers and fathers should be equal. The proportion of affected sisters does not differ from the proportion of affected brothers of the index case.

Expressivity and penetrance: An assumption of variable expressivity or low penetrance would be necessary to fit these data to the dominant pattern.

Genetic plus constant environmental factor: No observations were made in this study that might demonstrate the combination of a definite genetic pattern and a constant environmental factor determining the disorder.

B. Simple Recessive (Single Recessive Gene Substitution)

Affected parents: If this disorder were a recessive with single gene substitution the expected proportion of families with 0, 1 and 2 affected parents would be as shown in table 7 for 3 different assumed incidences of the disorder. There is poor agreement with the observed proportions, where 1-parent-affected families predominate; under recessive inheritance 0-affected parent families should predominate.

Affected sibs: When neither parent is affected, the expected number of affected sibs, when family size and the index case are included in the calculation, is 35.96 affected cases as compared with the observed number of 28 cases. This deviation is significant and does not support the hypothesis. For 1 affected parent the expected number is 64.8, compared with the observed number of 44; this discrepancy is significant. For 2 affected parents all children should be affected, against the 13 (61.9%) observed. These data do not fit the expectations of recessive inheritance.

C. Double Dominance (Double Dominant Gene Substitution)

Affected parents: 39.7% of families have no affected parent, and 48.3% have 1 affected parent. The double dominant pattern shows the proportion of families with no parents affected and those with 1 parent affected as in table 7. This fits the observed data better than does the recessive hypothesis. The expected proportions 61.50% and 63.41% deviate from the observed values. The others do not. The observed proportions of families with 2 affected parents is too high to fit the hypothesis, assuming random mating (10).

Affected sibs: For no affected parents, the numbers of cases calculated according to hypothesis, namely 35.9, 37.2, 38.6, are significantly higher than the observed number of 28. For 1 affected parent the numbers calculated from hypothesis are 43.6, 46.5 and 48.2, and only the last deviates significantly from the observed number of 40 (table 6). For 2-affected-parent

families there is close correspondence between the observed number of cases, 13, and the calculated expected numbers of 13.4, 13.9 and 14.2. These differences are not significant, but the numbers are small.

TABLE 6. COMPARISON OF OBSERVED AND EXPECTED NUMBERS OF SIBS WITH N.C.A.

For each genetic hypothesis, expected frequencies are corrected for sibship size and for necessary inclusion of at least one affected member.

(a) *Both Parents Normal*

SIZE OF SIBSHIP s	NUMBER OF SIBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED			
			Recessive $\dagger p = 0.25$	Double Dominant, with assumed incidence of		
				1% $p = 0.263$	3.6% $p = 0.277$	5.6% $p = 0.286$
1	1	1	1.000	1.0000	1.0000	1.0000
2	5	6	5.715	5.8080	5.9260	6.0100
3	2	2	2.594	2.6628	2.7420	2.7954
4	6	6	8.778	9.0696	9.4032	9.6240
5	2	3	3.278	3.4040	3.5460	3.6400
6	3	4	5.475	5.7060	5.9652	6.1347
7	2	2	4.040	4.2210	4.4240	4.5570
8	0	0	—	—	—	—
9	1	1	2.433	2.5506	2.6820	2.7675
10	1	3	2.649	2.7800	2.9260	3.0220
Totals	23	28	35.962	37.2020	38.6144	39.5506
Significance ratio, t			2.3	2.6	2.9	3.1

(b) *One Parent Affected*

SIZE OF SIBSHIP s	NUMBER OF SUBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED			
			Recessive or Dominant $\dagger p = 0.50$	Double Dominant, with assumed incidence of		
				1% $p = 0.2857$	3.6% $p = 0.3189$	5.6% $p = 0.3380$
1	2	2	2.000	2.0000	2.0000	2.0000
2	6	7	7.998	7.0968	7.3452	7.5048
3	8	10	13.712	11.0016	11.5992	11.9688
4	3	6	6.399	4.7364	5.0664	5.2644
5	5	7	12.905	8.9650	9.6950	10.1275
6	2	4	6.096	4.0356	4.3992	4.6152
7	1	1	3.528	2.2512	2.4696	2.5991
8	0	0	—	—	—	—
9	0	0	—	—	—	—
10	0	0	—	—	—	—
11	0	0	—	—	—	—
12	1	3	6.001	3.5208	3.9204	4.1580
Totals	28	40	58.639	43.6074	46.4950	48.2378
Significance ratio, t			4.1	1.0	1.7	2.1

TABLE 6—*Continued*

(c) *Both Parents Affected*

SIZE OF SIBSHIP s	NUMBER OF SIBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED*				
			Dominant †$p = 0.75$	Recessive $p = 1$	Double Dominant, with assumed incidence of		
					1% $p = 0.5816$	3.6% $p = 0.6016$	5.6% $p = 0.6140$
1	0	0	—	—	—	—	—
2	3	5	4.800	6.000	4.2618	4.3812	4.4706
3	2	4	4.572	6.000	3.7914	3.9270	4.0236
4	1	3	3.012	4.000	2.4132	2.5084	2.5752
5	1	1	3.754	5.000	2.9590	3.0805	3.1665
Totals.....	7	13	16.138	21.000	13.4254	13.8971	14.2359
Significance ratio, t.....			1.7	∞	0.2	0.5	0.7

* The expected number of affected sibs, for each genetic hypothesis, was calculated in accordance with principles and formulae given in references 7, 8, 9, 10. Gene frequencies used in evaluating these expected frequencies were based on assumed incidences of the disease of 1%, 3.6%, and 5.6% as suggested by a small populational survey (18); for the hypothesis of "double dominant" inheritance, the 2 dominant genes are assumed to be equally frequent.

† The expected proportion of affected offspring for each class of mating (0, 1, 2 affected parents) is designated as p.

TABLE 7. COMPARISON OF OBSERVED AND EXPECTED PERCENTAGES OF MATINGS UNDER HYPOTHESIS OF RECESSIVE INHERITANCE AND OF DOUBLE DOMINANT INHERITANCE

Values beneath percentages (in parentheses) are significance ratios (t) for differences between observed and expected percentages.

TYPE OF MATING	OBSERVED FREQUENCY OF MATINGS, PER CENT	‡EXPECTED FREQUENCY (PER CENT), ASSUMING					
		Recessive inheritance with incidence of			Double dominant inheritance with incidence of		
		1.0%	3.6%	5.6%	1.0%	3.6%	5.6%
Neither parent affected	39.7	81	65.47	58.45	42.71	36.29	32.71
		(*)	(*)	(*)	(0.5)	(0.5)	(1.1)
One parent affected	48.3	18	30.94	35.97	56.25	61.49	63.41
		(*)	(*)	(*)	(1.2)	(2.1)	(2.4)
Both parents affected	12.0	1	3.59	5.58	1.04	2.22	3.88
		(*)	(*)	(*)	(8.2)	(5.0)	(3.2)

* All expected percentages deviate significantly from the observed percentages under the hypothesis of recessive inheritance.

‡ For each of the 2 genetic hypotheses, the expected proportions of the 3 kinds of mating are calculated on the basis of gene frequency estimates evaluated for the three different assumed incidences of the disorder (18).

The observed proportion of affected siblings, then, is too low for the 0-parent-affected family but corresponds fairly well with the expected numbers in 1-parent-affected and 2-parent-affected families.

Sex proportions: The excess of mothers as compared to fathers does not fit this hypothesis.

D. Sex-Linked Heredity

Sex-linked recessive: This pattern should show: 1) no affected daughters of non-affected parents; 2) that when the mother is affected and the father not, all the sons should be affected and none of the daughters; 3) that when both parents are affected, all children should be affected.

The data (fig. 1) corresponding to these laws show: 1) 1 affected daughter in 42 daughters of non-affected parents; 2) of an affected mother and non-affected father, 32 of 65 sons are affected, and 8 of 33 daughters are affected; 3) 2 affected parents yield 21 affected and 13 non-affected children. The data obviously do not correspond to the pattern of recessive sex-linked heredity.

Sex-linked dominant: Clinical data (12) show about twice as many female patients as male patients. This is consistent with the possibility of the sex-linked dominant pattern, where approximately twice as many women are affected as men if the gene in question is relatively rare. The proportion of affected sons in this study is biased by the fact that all index cases are males; excluding them, the proportion of affected brothers is the same as affected sisters.

Affected parents: Every affected person should have at least 1 affected parent: This is not true in 34.8% of the cases here.

Affected sibs: Affected fathers with non-affected wives should have only affected daughters and normal sons. Figure 1 shows 6 affected sons of 12 and no affected daughters of 18 when the father is affected and not the mother. These data contradict the hypothesis of sex-linked dominant inheritance.

Analysis including cases of probable neurocirculatory asthenia and alcoholism

Table 8 shows that when analysis of data is made, including brothers, sisters and parents with 'probable N.C.A.' and alcoholism as cases of neurocirculatory asthenia (table 4—IV) there is close correspondence between the total observed number of affected cases and the total number expected from double dominant hypothesis. There were no significant deviations for no-parent-, 1-parent- and 2-parent-affected families. There were no significant deviations from proportions using gene frequency assumptions of 0.05, 0.1, and 0.13, closest correspondence being present for 0.05 gene frequency.

Single dominant or single recessive hypotheses do not fit the facts.

It is concluded that the possibilities suggested by these data should be taken seriously as a basis for further work; that the number of unproved assumptions in these calculations, however, should lead to caution in interpreting the results.

Testing the data of acute N.C.A. under various genetic hypotheses

Table 3 shows that it is suggestive but not definite that acute neurocirculatory asthenia runs in families.

For no parents affected there were 38 cases, 35 of which were index cases. The number expected by the single recessive hypothesis would be 47.5 and by the double dominant, with assumed gene frequency 0.13, 51.1, both of which are quite high. If the data are analyzed for the possibility of double

TABLE 8. COMPARISON OF OBSERVED AND EXPECTED NUMBERS OF SIBS WITH N.C.A., INCLUDING 'PROBABLE N.C.A.' AND 'ALCOHOLISM' AS AFFECTED

This table represents a reworking of the sibship analysis presented in detail in table 6, but reclassifying all parents and sibs by inclusion of 'probable N.C.A.' and 'alcoholism' cases among the affected. Only the totals (for sibships of all sizes) and the t-values are given here. The observed totals in tables 6 and 8 do not agree, owing to reclassification of parents as well as sibs.

(a) *Both Parents Normal*

SIBSHIPS (ALL SIZES)	NUMBER OF SIBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED			
			Recessive $p = 0.25$	Double Dominant, with assumed incidence of		
				1% $p = 0.263$	3.6% $p = 0.277$	5.6% $p = 0.286$
Totals	12	15	17.804	18.3780	19.0380	19.4785
Significance ratio, t			1.2	1.4	1.7	1.8

(b) *One Parent Affected*

SIBSHIPS (ALL SIZES)	NUMBER OF SIBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED			
			Recessive or Dominant $p = 0.50$	Double Dominant, with assumed incidence of		
				1% $p = 0.2857$	3.6% $p = 0.3189$	5.6% $p = 0.3380$
Totals	32	52	72.063	52.3010	55.9875	58.2010
Significance ratio, t			3.9	0.1	0.9	1.4

(c) *Both Parents Affected*

SIBSHIPS (ALL SIZES)	NUMBER OF SIBSHIPS n_s	NUMBER AFFECTED SIBS OBSERVED	NUMBER AFFECTED SIBS EXPECTED				
			Dominant $p = 0.75$	Recessive $p = 1$	Double Dominant, with assumed incidence of		
					1% $p = 0.5816$	3.6% $p = 0.6016$	5.6% $p = 0.6140$
Totals	14	29	35.144	46	28.9356	29.9864	30.7354
Significance ratio, t			2.2	∞	0.02	0.3	0.6

recessive gene hypothesis with an assumed $p = 0.0625$, the expected number of affected cases would be 37.7; for the triple dominant hypothesis, 40.53. For 1 parent affected, there are but few cases, 6 observed; 7.0 are expected from the double recessive hypothesis (p assumed to be 0.25), and 5.9 cases are expected from the triple dominant hypothesis (p assumed to be $\doteq 125$).

No conclusions can be drawn from these calculations. They suggest that

if *acute* N.C.A. is genetically determined, the pattern is closer to the triple dominant and double recessive pattern than it is to the simpler genetic patterns. Further observations and calculations are required for any definite conclusions about acute neurocirculatory asthenia.

DISCUSSION AND SPECULATION

The data, within the assumptions of the diagnosis, prove that the disorder runs in families. It should be emphasized that the definition of the disorder, its accurate diagnosis and its separation from or identification with other disorders are subject to the limitation that at present there are no conclusive, well-established objective diagnostic tests. It is possible that objective tests, as described in another report (12), may obviate the difficulty in future work; for the present, however, this is a definite source of uncertainty in work on all disease where the patient's symptoms and signs govern the diagnosis, and where more reliable tests such as specific objective tests, biopsy or autopsy abnormalities are not established.

Some of the unreliability of the symptom method of diagnosis was eliminated by using a systematic scheme of diagnosis (table 1) which was applied rigidly to relatives of patients and controls alike. Although this provides more precision it does introduce an artificial rigidity to the problem of clinical diagnosis. However, the fact that the proportion of diagnoses of N.C.A. made by "clinical impression" approximated closely the systematic scheme of diagnosis led to the conclusion that both approaches yielded similar diagnostic information.

Further, most of the data came indirectly via the patient's verbal description of a relative. The question arises whether the relatives really had those symptoms or whether the patients, either through such processes as false emphasis or false memory, or through ideas associated with being discharged from military service, might have assigned to relatives symptoms which in fact did not exist. The incomplete study comparing second-hand with first-hand information showed good agreement in diagnoses from both sources; the discrepancy is on the side of more affected in the examined group. Also, it should be added that relatives were examined directly in a second study (18) done in this laboratory. That study demonstrated that on direct examination 48.6% of 37 sons and daughters of civilian families with neurocirculatory asthenic parents were affected. Thus, both indirect and direct evidence show that there is high familial prevalence of the disorder.

Did these patients suffer from the same disorder as the patients referred to by various authors whose opinions are summarized in table 9 under different diagnostic terms? As far as those authors describe their cases clinically their patients resemble the cases reported here. Since most of the authors presented the minimum of diagnostic details no definite conclusion about the identity or non-identity of the disorder they were describing with that of this report

TABLE 9. OPINIONS AND CONCLUSIONS CONCERNING THE FAMILIAL PREVALENCE OF NEUROCIRCULATORY ASTHENIA (ANXIETY NEUROSIS, EFFORT SYNDROME)

DATE	AUTHOR	TERMINOLOGY	TOTAL NUMBER OF CASES REPORTED	WERE CASES STUDIED FROM FAMILIAL STANDPOINT?	ARE CONCLUSIONS BASED ON DATA PRESENTED?
1869	Beard (19)	Nervous Exhaustion (Neurasthenia)	0	No	No
"Hereditary descent terribly predisposes to neurasthenia."					
1871	Da Costa (20)	Irritable Heart	200	No	No
No comments on familial appearances.					
1895	Freud (21)	*Angstneurose*	0	No	No
"... In some cases no etiology can be readily ascertained ... in such cases it is seldom difficult to demonstrate a marked hereditary taint. ..."					
1899	Savill (22)	Neurasthenia	0	No	No
"general hereditary taint"					
1902	Hartenburg (23)	*Névrose d'Angoisse*	58	No	No
One family had nervousness in mother and father.					
1907	Savill (24)	Neurasthenia	205	No	No
"... heredity as a predisposing cause of neurasthenia may and does sometimes act. ..."					
1911	Ballet (25)	Neurasthenia	0	No	No
"... The proportion of neurasthenics in whose antecedents one finds hereditary taints more or less marked may be estimated at 40%."					
1917	Heckel (26)	*Névrose d'Angoisse*	0	No	No
"There is not the least doubt of familial predisposition."					
1918	Lewis (27)	Effort Syndrome	558	No	No
"One of the largest groups is that of constitutional weakness, nervous, or physical or both."					
1918	Oppenheimer, Levine, Morrison, Rothschild, St. Lawrence, Wilson (28)	Neurocirculatory Asthenia	558	No	No
"... must lay stress on the importance of a complete anamnesis ... even at times including family history."					
1918	Oppenheimer, Rothschild (29)	Irritable Heart	100	Yes	Yes
Family history shows that there is more nervousness, alcoholism, irritability, insanity, tuberculosis, epilepsy and stigmata in parents than there is in family history of Wolfsohn's controls.					
1918	Robey and Boas (30)	Neurocirculatory Asthenia	89	No	No
"The vast majority of the patients give a family history of nervous disorder."					
1925	Myerson (31)	Neurasthenia	0	No	No
"... that 'some' people 'are' predisposed to neurasthenia in that from the first days of their lives they showed lowered energy and endurance, irritability, emotional unrest, etc. ..."					
1940	Lewis (32)	Effort Syndrome	860	No	No
"One of the largest groups is that of constitutional weakness, nervous or physical or both ..." "Many show defective physical development ... The defects are certainly derived from both hereditary and acquired sources."					
1941	Wood (33)	Da Costa's Syndrome	265	Yes	Yes
41.9% of patients have family history of "neuroses" or "nerves" as compared with 9.6% in controls.					

TABLE 9—*Continued*

DATE	AUTHOR	TERMINOLOGY	TOTAL NUMBER OF CASES REPORTED	WERE CASES STUDIED FROM FAMILIAL STANDPOINT?	ARE CONCLUSIONS BASED ON DATA PRESENTED?
1942	Brown (34)	Anxiety State	63	Yes	Partly
Anxiety state appeared in 21.4% of parents and 12.3% of siblings as compared with 0% and 0% respectively in controls. Concludes that three types of neurosis, i.e. "anxiety state," "hysteria" and "obsessional state" are "genetically related," although his published data do not support this.					
1943	Slater (35)	Anxiety Neurosis	647	Yes	Yes
56.7% of patients had "general positive family history," i.e., there was definite neurotic illness, psychosis, epilepsy, psychopathy (drunkenness, shiftlessness, violent or brutal habits). No data on control subjects. Concludes: "The neurotic constitution is then a useful hypothesis. . . ."					
1946	Cohen, Badal, Johnson, Chapman, White (1)	Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis.	70	Yes	Yes
The disorder occurred in 47% of mothers, 40% of fathers and 13.2% of brothers and sisters of patients as compared with 0%, 4.9% and 0% in normal controls.					
1948	Wheeler, White, Reed, Cohen (18)	Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis	50	Yes	Yes
Prevalence in sons and daughters of patients is 48.6% as compared with prevalence of 5.6% in general population of 234 healthy controls.					
1948	Cohen, White, Johnson (12)	Neurocirculatory Asthenia, Anxiety Neurosis, Effort Syndrome; Chronic and Acute Types	67	Yes	Yes
Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syndrome) occurs in 18.5% of fathers, 58.0% of mothers and 12.6% of brothers and sisters of patients with chronic neurocirculatory asthenia in contrast to no cases in fathers, mothers, brothers and sisters of 54 control subjects.					

can be reached. It seems likely, as far as it can ever be settled, that the various authorities were referring to the same kind of disorder.

It will be noted from table 9 that little or no data were presented to support the conclusions. It should also be noted that most of the authors did not comment on the occurrence in families of the disorder itself but emphasized "hereditary taint," nervousness, family history factors other than the disorder itself, such as nervousness, alcoholism, irritability, insanity, tuberculosis and epilepsy, "neuroses" or "nerves," psychopathy, constitutional weakness and other assorted factors believed by various authors to be relevant. Those terms have been largely undefined and therefore not particularly useful. This study was directed chiefly at discovering whether neurocirculatory asthenia itself occurred in the relatives of such patients, not at accessory findings.

The term "constitutional" was avoided in this report as a loose and unserviceable term. It has been used by some authors who did not define it. Others

defined it, but so broadly as to render it meaningless (36, 37). The definitions also differ from author to author (28, 32, 35, 38). Pearl (39) points out that there are two general usages, a "totality" concept and a "genetic" concept, and states in referring to Günther (40), in whose paper 70 definitions are recorded, that "constitution" seems to have "nearly. . .as many meanings, or shades of meaning, as the number of persons who have written about it." It is recommended that "constitution" and "constitutional," both the terms and many of the ill-defined concepts implied by them, be abandoned as having too many meanings to have any meaning at all.

The major purpose of this study was to establish whether the disorder neurocirculatory asthenia runs in families. This is quite a different matter from the study of the familial prevalence of "general neuropathic traits," or the familial prevalence of sickness in general, or other specific medical, psychiatric or neurologic diseases, although those facts may be related and important. The data in these patients on the prevalence of other diseases were limited but showed that there was no marked familial prevalence of epilepsy, disease leading to psychiatric hospital care, or heart disease in these cases (1). In addition, the study of 37 children of neurocirculatory asthenia (anxiety neurosis, effort syndrome) parents (18) revealed no evidence of hysteria, depression or obsessional neurosis in children of parents with N.C.A. although there was a high prevalence of N.C.A. in those children. This agrees with the data of Brown (34) but does not support his conclusion of "genetic relationship between the 'anxiety state' and the two other 'psychoneuroses' ('hysteria' and 'obsessional state')." The observations presented by that observer do not support his conclusions since his data do not show that hysteria or obsessional neurosis and depression are more prevalent statistically in relatives of "anxiety state" patients than they are in relatives of control subjects.

The literature (table 9) reveals that the idea that this disorder runs in families is not a new idea, and in the more recent literature (1, 12, 18, 34) data are presented to support that point of view. The previous literature does not comment on the familial prevalence of *acute* neurocirculatory asthenia. The present study suggests a probable familial tendency.

Although the data presented here show clearly that this disorder runs in families, they do not settle the problem of whether that is due to a hereditary factor, or to some environmental household factor, or to both. This type of study could not answer that question conclusively. The random appearance of cases as occurs here in a sibship has been described (5, 34) as evidence for heredity. This obviously is not conclusive.

If this disorder were a hereditary disorder what pattern does it follow best? It does not fit any pattern exactly. Closest fit is to the dominant or double dominant patterns. However, the calculations made depend on certain assumptions which may not apply in this study. The general prevalence of the

disorder should be known; this was approximated in this study at 1%, 3.6% and 5.6% for calculation purposes. A general population sample (18) gave the latter figure. Two surveys, one American (41) and one British (42), would place the top limit for prevalence of all neuroses at 2%. The genetic calculations made assume non-assortative mating (10). This seems improbable in human beings; the high proportion of parents with affected spouses suggests further that this did not occur. There are, incidentally, various possible interpretations for the high proportion of parents with affected spouses, but no crucial data were at hand to explain the finding.

The number of observed cases should be lower than the expected number in this study. First, information from relatives is said (43) to yield a lower number of cases than that actually observed on direct examination; secondly, the onset of this disorder may occur in many cases (44) in the second and third decades of life. Since all subjects over 18 were included, there should be a lower number of observed cases than demanded by any genetic hypothesis. No attempts were made in this study to correct for that factor. The data, when analyzed, suggest that if a hereditary factor were important in the disorder it might be on the basis of a Mendelian dominant with low penetrance, which has been claimed by one observer (45) to be the most common mechanism in human disease, or on the basis of two independent and complementary genes (double dominant) whose presence is not manifest without the other.

Further study is necessary to 1) prove that the disorder is or is not on a hereditary basis; 2) prove that it does follow a definite genetic pattern or assortment of patterns; 3) decide whether probable and alcoholic patients should be included; 4) clarify the situation with regard to the acute neurocirculatory asthenia.

The question arises whether the fact that the disorder runs in families can be explained on environmental household factors. No data were obtained in this study that bear crucially on that point. In an extensive study of neurocirculatory asthenia (1) various possible environmental factors were studied. No evidence of infection (12) was found in the patients. Home and personal problems were not present significantly more in patients than in healthy controls (1). A variety of factors was associated with exacerbations of the illness (1), none giving any clue as to specific environmental cause. The possibility of simple imitation of a sick relative by another can be excluded since the symptoms (table 10) are not identical from case to case in the same family. It is sometimes assumed (46) that disorders of this type are "psychogenic" in origin. No data were elicited that proved that theory, nor have such data been presented by anyone. As a matter of fact, there is no clear-cut evidence to date that any disease is "psychogenic," i.e. caused by personal problems and emotion-provoking situations and experiences.

Before accepting, without adequate evidence, any one idea as to the cause

TABLE 10

SUMMARY OF SYMPTOMS AND DIAGNOSES IN ALL RELATIVES IN ALL FAMILIES CONTAINING CASES OF NEUROCIRCULATORY ASTHENIA

Each paragraph refers to a family. A family consists of the index case, his parents, brothers and sisters. The number heading each paragraph refers to the case number as illustrated in figure 1. Synopsis of symptoms is given, using for the most part the words of the index case.

A. FAMILIES OF MEN WITH CHRONIC NEUROCIRCULATORY ASTHENIA

1. Father: nervous, dizzy, dizzy spells on running and excitement, palpitation, not strong, couldn't work hard, shortness of breath, same trouble as patient, N.C.A. Mother: always nervous, easily upset, dizzy spells, nervous shocks, numb hands, always sick, quit work because of fatigue, never strong, same trouble as patient, N.C.A. Sister: dizziness when nervous, palpitation,? thyroid, weakness and lost weight when job got on her nerves, same trouble, N.C.A. Brother: the patient.

2. Second brother: the patient.

3. Father: nervous inwardly, catches breath, N.C.A. Mother: goes to pieces, can't sleep or eat when nervous, can't stand heart when excited, high blood pressure, when young had weak, black spells in the morning, sweats, N.C.A. Third brother: the patient.

4. Mother: nervousness, faints, easily excited, easily angered, sighs, pain in heart, low blood pressure, gasps for breath, same trouble, N.C.A. First brother: the patient. Second sister: excitable, took iron, afraid of the dark and of walking on slippery streets, probable N.C.A.

5. Father: faint, dizzy spells, weak, no N.C.A. First brother: the patient.

6. Third sister: shook, nervous breakdown, passed out, same trouble as patient, pounding of the heart, died at age of 29 of heart trouble, N.C.A. Third brother: the patient.

7. Mother: high blood pressure, no N.C.A. Brother: the patient. Sister: fears death, no N.C.A.

8. Father: high blood pressure, no N.C.A. Mother: nervous, easily excited, worried about heart, weak feeling, N.C.A. First sister: crying spells, nervous, anorexia, no N.C.A. First brother: the patient. Second brother: tremor of hands, no N.C.A.

9. Mother: nervous, migraine headaches, no N.C.A. First brother: the patient.

10. Mother: nervous, heart disease, high blood pressure during menopause, shortness of breath, N.C.A. First brother: the patient.

11. Third brother: the patient.

12. Father: pain in chest in 1918, probable N.C.A. First brother: the patient.

13. Father: "weak lungs," no N.C.A. Mother: dizzy spells, must lie down all the time, couldn't work because of condition, N.C.A. First brother: shaky, nervous, no N.C.A. Second sister: faints, same trouble, shortness of breath, N.C.A. Second brother: the patient.

14. Father: faints, anemic, always cold, low blood pressure, arthritis, no N.C.A. Mother: nervous, dizziness, bad temper, migraine, high blood pressure, palpitation, gas around heart, many doctors, N.C.A. First brother: the patient. Fourth brother: high-strung, nervous, shy, no N.C.A.

15. Father: shy, dizziness, temper, palpitation, pains around heart, ulcer, N.C.A. Mother: "shock," headaches, dizziness, high blood pressure, no N.C.A. First brother: the patient. Second brother: shy, secretive, no N.C.A. Third brother: very nervous, no N.C.A.

16. Father: nervous, no N.C.A. Mother: dizzy spells, nervous, irritable, restless, headaches, tense, upset, pains in the heart, breathing trouble, stomach trouble, N.C.A. First sister: worries, nervous, tense, burning around heart, probable N.C.A. First brother: nervous, faints a lot, stomach trouble,? ulcer, probable N.C.A. Second brother: the patient. Third brother: irritable, no N.C.A. Fourth brother: nervous, no N.C.A.

17. Mother: faints, from excitement, nervous, nervous breakdown, hysterics, dizzy, headaches, high blood pressure, gasps for breath, N.C.A. First brother: discharged from army for headaches and "pernicious anemia," faints, dizzy, shy, bad temper, nervous breakdown, N.C.A. Second brother: the patient.

18. Father: headaches, nervous,? migraine, heart disease, kidney trouble, high blood pressure, same trouble as patient, short of breath, N.C.A. Mother: nervous, headaches, worried about disease,

TABLE 10—*Continued*

fainting, pain in chest, "asthma," trouble in breathing, kidney trouble, can't work much, N.C.A. First brother: the patient. Second brother: heart disease, kidney trouble, no N.C.A. Third brother: nightmares, sleeping spells, "overgrown" heart, heart disease, heart attacks, pains in chest, N.C.A. Third sister: nervous trouble, restless, didn't want noise, weakness, weak spells, N.C.A.

19. Father: nervous, short of breath all life, same trouble, N.C.A. Mother: nervous, cries, nervous breakdown when patient injured, "weak heart," "murmur," short of breath all of life, tired, weak, N.C.A. Twin one: the patient. Twin two: headaches, pains in chest, breathing trouble, asthma, "different" from the patient, N.C.A.

20. First brother: nervous, pain in heart as child, heart attacks, short of breath, couldn't get breath, runs and works hard, N.C.A. Second brother: the patient.

21. Father: nervous, headaches, afraid to drive, excitable, nervous breakdown, same trouble, N.C.A. Mother: choking, nervous, faints easily, heart trouble, pains in heart, gas pains, cured tuberculosis, N.C.A. Third brother: the patient.

22. Mother: neuritis, no N.C.A. First brother: out of the army for murmurs, heart trouble, no N.C.A. Second brother: the patient.

23. Mother: nervous, shaky in crowds, on excitement, always worried, heart trouble, pains in chest, pains in stomach, winded on short walks, tired on short walks, N.C.A. First brother: the patient. Third sister: shakiness, nervousness, "gets the shakes," not well, "overactive" thyroid, N.C.A.

24. Father: headaches, no N.C.A. Mother: heart attacks, high blood pressure, no N.C.A. Second brother: the patient.

25. Father: nervous, excitable, dizzy, faints, same trouble as patient, N.C.A. Mother: faints, nervous, dizzy spells, bothered by noise, many operations, can't work, same trouble as patient, N.C.A. Second brother: the patient.

26. Father: low blood pressure, sinus, no N.C.A. Mother: nervous breakdown, no N.C.A. First brother: the patient.

27. Father: excited, angry, nervous, chest pains, stomach pains, coughs, can't get breath, not in good health, probable N.C.A. Mother: nervous, faints, shakes, worries, cries, pains in head, "hot" blood pressure, can't do own house work, can't stand in OPD line, gets weak, feels bad, N.C.A. First brother: the patient. Second brother: heart trouble, something sticking in chest, pain in the chest, after football, had to sit down, probable N.C.A.

28. Mother: nervous breakdown, no N.C.A. Brother: the patient. Sister: excitable, no N.C.A.

29. Father: nervous, angers easily, worries, restless, impatient, no N.C.A. Mother: fear of lightning, thin, not strong, bleeding hemorrhoids, probable N.C.A. First brother: faints, restless, dizziness, same as patient, worse than patient, N.C.A. Third brother: worries a lot, short of breath on talking, N.C.A. Sixth brother: the patient. Second sister: frail, many colds, no N.C.A. Third sister: nervous, highstrung, worries, faints, excitable, probable N.C.A.

30. Father: migraine, nervous, insomnia, pains in chest, stomach trouble, N.C.A. Mother: nervous, highstrung, skinny, anemic, vomiting, fast heart, nervous heart attacks, heart disease, breathing trouble, shortness of breath, can't work, stomach trouble, N.C.A. First brother: the patient. Second brother: headaches, hospitalized in army for nervousness, N.C.A. Third brother: headaches, nervous, thin, insomnia, pain in chest, shortness of breath, N.C.A.

31. Father: irritable, stomach trouble, tires easily, no N.C.A. Mother: stomach trouble, never healthy, vomiting, no N.C.A. First brother: the patient.

32. Fourth brother: the patient.

33. Mother: wheezing spells, short of breath, no N.C.A. First brother: the patient.

34. Father: headaches, pain in heart, breathlessness, doctor told him not to work but unable to stop, probable N.C.A. Mother: headaches, faints, dizzy spells, blood goes to head, high blood pressure, N.C.A. Second brother: the patient.

35. Father: pain in chest, short of breath when up and down stairs, throat not good, no N.C.A. Mother: nervous, worries, headaches, high or low blood pressure, weak spells, sick all life, poor health, obese, N.C.A. First sister: nervous, upset, same trouble, N.C.A. First brother: nervous, faints a lot, probable N.C.A. Second brother: the patient. Third brother: 4-F for ears, no N.C.A.

TABLE 10—*Continued*

36. Mother: nervous, worries, high blood pressure, same trouble, N.C.A. First brother: the patient. Sister: headaches, high blood pressure, no N.C.A.

37. Father: nervous, irritable, fears,? heart trouble, can't work, probable N.C.A. Mother: worries, headaches, dizziness, weak spells, goes to bed and rests, high blood pressure, N.C.A. First sister: nervous, anemic, invalid, N.C.A. Second brother: the patient.

38. Mother: nervous, short of breath, cries easily, trouble something like his, N.C.A. Only child: patient.

39. Father: nervous, irritable, tired, run down, lost pep, anorexia, no N.C.A. Mother: dizziness, nervous, hysterics, cries easily, palpitation, stomach trouble, takes heart pills, takes nerve pills, N.C.A. Second brother: nervous, faints, constipated, probable N.C.A. Third brother: twin, the patient. Second sister: twin, nervous breakdown, nervous, faints, palpitation, tight throat, N.C.A. Third sister: headaches, no N.C.A.

40. Mother: faints, headaches, nervous, heart trouble, N.C.A. Second sister: nervous breakdown, headaches, fainting, palpitation, fast-beating heart, heart trouble, N.C.A. Third brother: the patient.

41. Second brother: the patient.

42. Mother: nervous, short of breath, headaches, dizzy spells, palpitation, can't work much, takes life easy, N.C.A. Brother: the patient.

43. Mother: nervous breakdown during menopause, high blood pressure, no N.C.A. Brother: the patient. Sister: nervous, no N.C.A.

44. Mother: nervous, worries, palpitation, on verge of nervous breakdown, same trouble, N.C.A. Brother: the patient.

45. First sister: tired now, can't work, no N.C.A. Second brother: the patient.

46. Father: worries, nervous, pain in heart, breathing trouble, N.C.A. Mother: nervous, worries, insomnia, faints, hot flushes, high blood pressure, no N.C.A. First sister: nervous, weak heart, probable N.C.A. Second sister: nervous, no N.C.A. Brother: the patient.

47. First brother: the patient.

48. Mother: nervous, faints, palpitation, trouble with heart, higher blood pressure at one time, shortness of breath all life, doesn't work too hard, N.C.A. First brother: the patient.

49. Father: pains in heart, nervous, no N.C.A. Second sister: nervous, headaches, no N.C.A. Fourth brother: the patient.

50. First sister: highstrung, no N.C.A. First brother: the patient. Second sister: highstrung, no N.C.A. Father: "athletic heart," took it easy for 10 years—unknown.

51. Mother: nervous, fainting, palpitation, weak spells, weight loss, N.C.A. First brother: the patient. First sister: headaches, irritable, sweating, flushed face, thin,? thyroid, weakness, intolerance to effort, exhausted, N.C.A.

52. Father: highstrung, no N.C.A. Mother: nervous, afraid of water, same headaches as patient, palpitation, tired, N.C.A. First brother: highstrung, nerved up easily, nightmares, no N.C.A. Second brother: the patient.

53. Father: headaches, no N.C.A. Mother: pain in chest, weak heart, short of breath like patient, can't work too hard, N.C.A. First brother: the patient. Second sister: dizzy, nervous, rests, fainting spells when scared, has to lie down, sickly, same trouble as patient, N.C.A. Third sister: thyroidectomy, heart disease, choked by lump in throat, probable N.C.A.

54. Father: nervous, highstrung, no N.C.A. Mother: nervous, headaches, nervous indigestion, no N.C.A. First sister: upset easily, shakes and cold, highstrung, no N.C.A. First brother: the patient.

55. Father: irritable, no N.C.A. Mother: nervousness, faints, high blood pressure, same trouble, breathing trouble, N.C.A. Only child: the patient.

56. Father: nervous, some kind of heart trouble when angry, N.C.A. Second brother: the patient.

57. Father: irritable, no N.C.A. Mother: faint, weak, dizzy, excitable, headaches, nervous breakdown, same trouble, N.C.A. Second brother: headaches, no N.C.A. Second sister: headaches, nervousness, nausea, no N.C.A. Third brother: the patient.

58. Father: irritable, excitable, worried, needed rest because of nervous fatigue, N.C.A. First brother: the patient. Third brother: same as patient, N.C.A. Fifth brother: same as patient, N.C.A.

59. Mother: faints a lot, dizzy spells, worries, nervous, weak, N.C.A. First sister: nervous, jumpy,

TABLE 10—*Continued*

nervous breakdown, weak, same trouble, N.C.A. First brother: nervous, weak, no N.C.A. Second brother: the patient. Third brother: same trouble, can't do hard work, small, thin, N.C.A.

60. Father: nervous, faints, health delicate, probable N.C.A. Mother: dizzy spells, squeezing pain, heart trouble, always short of breath, N.C.A. Second brother: the patient. Sister: treated for underweight, nervous, probable N.C.A.

61. Mother: nervous, no N.C.A. First brother: the patient. Second brother: rejected for high blood pressure, no N.C.A.

62. Mother: nervous, nervous breakdown, same trouble, tires easily, obese, too much fat around heart, N.C.A. Only child: the patient.

63. Father: highstrung, nerves, heart attack one year ago, no N.C.A. Mother: migraine, sick at time, fallen stomach, weak earlier, probable N.C.A. Only child: the patient.

64. First brother: dizziness, faintness, heart attacks, pains in heart, N.C.A. First sister: nervous, worries, no N.C.A. Third brother: the patient.

65. Father: nervous, nervous breakdown, stomach trouble, no N.C.A. Mother: high blood pressure, short of breath, probable N.C.A. First sister: short of breath, no N.C.A. Second brother: heart trouble because of alcohol, no N.C.A. Third brother: the patient.

66. Second brother: the patient. Third brother: same trouble, sharp pains, high blood pressure,? "neurosis," N.C.A.

67. Second sister: high blood pressure, heart bad, no N.C.A. Fourth brother: the patient.

B. FAMILIES OF MEN WITH ACUTE NEUROCIRCULATORY ASTHENIA

1. Father: nervous, excitable, no N.C.A. Brother: the patient.

2. Mother: heart trouble, healthy until patient born, tired, weak, rested a lot, N.C.A. Third sister: nervous, no N.C.A. First brother: faints, excitable, shakes, angry, nervous, same trouble, N.C.A. Second brother: highstrung, nervous breakdown from overwork, restive, probable N.C.A. Third brother: the patient.

3. Mother: heart disease, pain, run down, liver, nitroglycerine, N.C.A. Third brother: the patient.

4. Mother: excitable, worries, no N.C.A. Only child: the patient.

5. First brother: nervous, no N.C.A. First sister: sensitive, easily hurt, no N.C.A. Second brother: the patient. Second twin: fainting spells, not robust, weak, rests, probable N.C.A.

6. Only child: the patient.

7. First brother: breathing trouble, no N.C.A. Second brother: the patient.

8. Mother: nervous, no N.C.A. Only child: the patient.

9. Brother: the patient. Sister: nervous breakdown, no N.C.A.

10. Mother: nerves shot, nervous breakdown, hysterical, shaking, no N.C.A. Second brother: the patient.

11. Third brother: the patient.

12. Father: sensitive, irritable, no N.C.A. Mother: nervous, sickly with nerves, same trouble, smothering sensation, palpitation, heart attacks, heart condition, N.C.A. Brother: the patient.

13. Second brother: the patient.

14. Mother: dizziness, nervous, shaky, "might have same trouble," N.C.A. First brother: rejected by Navy for nervousness, probable N.C.A. Second brother: the patient.

15. Mother: nervousness, no N.C.A. Second brother: the patient.

16. Mother: nervous, fainting, sickly, no N.C.A. First brother: the patient.

17. Mother: nervous, faints, cries, afraid of hospitals, indigestion, no N.C.A. Second brother: the patient.

18. First brother: the patient.

19. First sister: faints, no N.C.A. Brother: the patient.

20. Only child: the patient.

21. First brother: the patient.

22. First brother: the patient.

TABLE 10—*Continued*

23. Father: heart pain from gas, no N.C.A. Mother: nervous, worries, almost had a nervous breakdown, no N.C.A. First brother: nervous, worries, no N.C.A. Third brother: the patient.

24. Mother: breathing trouble, no N.C.A. Sister: nervous, jumpy, doesn't work, probable N.C.A. First brother: the patient.

25. Brother: the patient.

26. Third brother: the patient.

27. Third brother: the patient.

28. Brother: the patient.

29. First brother: the patient.

30. First brother: the patient.

31. Second brother: the patient.

32. Father: smothering spells, sat up to breathe, no N.C.A. Mother: nervous, highstrung, excitable, tired, weak, probable N.C.A. Second brother: the patient. Second sister: nervous, no N.C.A.

33. Brother: the patient.

34. Second brother: the patient.

35. Father: fainted once, tires easily, hurt, no N.C.A. Mother: easily upset, nervous, flushes, insomnia, tires easily, rests a lot, weak, probable N.C.A. Only child: the patient.

36. Mother: highstrung, excitable, worries, no N.C.A. First sister: nervous, no N.C.A. Second sister: nervous, no N.C.A. Second brother: the patient. Third brother: same trouble, shaky after action, N.C.A.

37. Mother: nervous breakdown, no N.C.A. Only child: the patient.

38. Third brother: nervous, palpitating heart, grouchy spells, 4-F, N.C.A. Second brother: the patient.

39. Father: heart attacks for years, no N.C.A. Mother: nervous, faints, "neuraligia" of the heart, no N.C.A. First sister: faints, nervous, pain inside, tired, weak, liver trouble, probable N.C.A. Brother: the patient. Second sister: faints, no N.C.A.

40. Mother: headaches, afraid, several nervous breakdowns, probable N.C.A. Brother: the patient. Sister: jittery, nervous, no N.C.A.

41. Father: restless, worries, spasm, nervous cardiac condition, N.C.A. Mother: nervous vomiting spells, anemic, tired, no N.C.A. Brother: the patient.

42. Second brother: the patient.

43. First brother: the patient.

44. Mother: headaches, nervous, no N.C.A. First sister: faints, dizzy, nervous breakdowns, couldn't ride in buses, couldn't go in crowds,? same trouble, N.C.A. Brother: the patient.

C. FAMILIES OF MEN IN CONVALESCENT CONTROL SERIES

7. Mother: faints, gets upset, breathing trouble, can't work at home, N.C.A. First brother: the control, faintness, palpitation, anorexia, N.C.A. Second brother: discharged because of nervousness, probable N.C.A.

8. Mother: nervous, breathing trouble, same trouble, N.C.A. First sister: nervous, weak when works, probable N.C.A. Second sister: palpitation, no N.C.A. Third brother: the control, headaches, dizzy spells, dizziness, nervous, flushes, apprehension, palpitation, throbbing, breathlessness, syncope, inability to get a satisfactory breath, weakness, N.C.A.

17. Mother: nervous, went to pieces, cried a lot, hysteria, high blood pressure, breathing trouble, asthma and heart, N.C.A. Only child: the control, nervousness, nervous chill, apprehensive, dizziness, palpitation, smothering, vascular throbbing, weakness, anorexia, N.C.A.

D. FAMILIES OF MEN IN HEALTHY CONTROL SERIES

22. Third brother: the index case.

37. First brother: the index case.

of this disorder and its high familial prevalence, it is well to examine the literature. There one finds a rich assortment of varied ideas and theories, usually with no substantial data to support them, about the cause, "etiologic factors" and mechanisms leading to the disorder or its symptoms.

An incomplete sample of these conclusions as to cause, "etiologic factors" and mechanisms includes the following: "Cardiac muscular exhaustion and atrophy," Hartshorne, 1864 (47); "bad adjustment of the pack and accoutrements," Maclean, 1867 (48); due to "progress and refinement . . . central nervous system becomes dephosphorized," Beard, 1869 (19); "fevers, diarrhea, hard field service, wounds, injuries," Da Costa, 1871 (20); "waste of nerve tissue in excess of repair," Beard, 1880 (49); "wear and tear of the nervous system" due to "cares," "responsibilities," "anxiety," "inquietude," Flint, 1884 (50); "autointoxication, due to pyorrhea alveolaris, fermentation dyspepsia, or intestinal putrefaction," I. G. Cobb, 1915 (51); "predominant etiologic factor . . . is infection of one kind or other," Lewis, 1917 (52); "masturbation or accumulated pollutions" and "such factors as coitus interruptus," Freud, 1920 (53); the idea "I want to use my genital organs for pregenital purposes" floods the affected "organ representations" with uncontrolled "libido," Reich, 1926 (54, 57); anxiety attack represents "phantasy of giving birth," H. Deutsch, 1930 (55, 57); "visceroptosis," Archard, 1934 (56); in "cardiac neurosis . . . the heart represents the penis," Fenichel, 1934 (57); "chronic undulant fever," Thames, 1935 (58); "fatigue of the nervous system" due to "nervous overstrain" and "infections" and associated with "imperfect oxygenation of the blood," Haldane and Priestley, 1935 (59); "symptoms of these patients are not mentally determined or removable by analysis, but . . . they must be regarded as direct toxic consequences of disturbed sexual chemical processes," Freud, 1935 (60); "low blood chlorides," O. Johnson, 1936 (61); "allergic manifestations," Marshall and Tarwater, 1938 (62); "respiratory alkalosis," Soley and Shock, 1938 (63); the "energy-controlling organs" . . . "brain-adrenal-sympathetic system," Crile, 1940 (64); "focal infection" . . . "teeth, sinuses," Baach, 1940 (65); infections such as rheumatic fever, amoebic dysentery, bacillary dysentery, Parkinson, 1941 (66); "central stimulus is emotional and is commonly the result of fear," Wood, 1941 (33); "hyper- and hypokinemic circulation," Starr, 1942 (67); "Graves' syndrome," Moschowitz and Bernstein, 1944 (68); "hypoglycemia," Greene, 1944 (69); "small heart," Master, 1944 (70); "the emotions," Strong, 1946 (71); "free floating anxiety" or "somatization reaction," Veterans Administration, 1947 (72); "cause or causes are unknown," Cohen, White, Johnson, 1948 (12).

There is, then, no obvious established cause or mechanism, which explains the disorder as yet. It could be useful to apply the knowledge that this disorder runs in families. This fact can be used as an aid in diagnosis in civilian medicine. If a reliable family history could be obtained under circumstances attendant to military medicine, it might be helpful in problems relating to diagnosis, selection and disposal of patients.

Knowledge as to whether heredity is the important factor or a minor factor determining "susceptibility" or no factor at all would be important in planning the emphasis of further studies. And if evidence suggests "inherited susceptibility," emphasis might be placed on search for other evidence of expressivity of the disorder. Then special studies could be planned on possible precipitating stimuli in "susceptible" individuals. It is commonly believed by many physi-

cians that a hereditary disorder is hopeless as far as treatment is concerned. The facts do not support this notion. Some of the most treatable of diseases—pernicious anemia, diabetes, periodic family paralysis, thyrotoxicosis—are believed (73, 74) to be on a hereditary basis. This suggests that in some instances hereditary disease may represent lack of a single substance which can be efficiently replaced.

No amount of speculation will resolve the problem further. The facts remain that the disorder runs in families, that no environmental cause has been discovered, that the family patterns suggest, but not perfectly, the pattern of Mendelian dominance, with single or double gene. Further study is necessary in order to get the right answer or answers.

CONCLUSIONS

1. There is a high prevalence of neurocirculatory asthenia (N.C.A.) in fathers, mothers, brothers, sisters and families of patients with neurocirculatory asthenia (anxiety neurosis, effort syndrome) as compared with that in relatives of control subjects.

2. The prevalence of the disorder is high in relatives of patients with *chronic* N.C.A.; the proportion of affected fathers is 17.5%, of mothers 54.8%, of brothers 13.3%, of sisters 12.1% and of families 67.2%.

3. As compared with chronic N.C.A., there is little N.C.A. in fathers, mothers, brothers, sisters and families of patients with *acute* N.C.A.

4. Only one case of N.C.A. was found in fathers, mothers, brothers and sisters of control subjects lacking the disorder.

5. In families of chronic N.C.A. patients, when neither parent is affected 27.5% of the offspring are affected, when one parent is affected 37.7% are affected, when both parents are affected 61.9% are affected.

6. In families of N.C.A. patients more mothers, 54.8%, have N.C.A. than do fathers, 17.5%.

7. Analysis of the data for chronic N.C.A. suggests that the prevalence of the disorder approximates the pattern of Mendelian dominance, single or double gene, in some features.

8. There is a high prevalence of alcoholism in fathers of patients with N.C.A. as compared with fathers of controls. The possibility that these alcoholic fathers represent cases of N.C.A. must be considered.

9. When 'probable N.C.A.' and alcoholism are included as cases of neurocirculatory asthenia, the pattern of occurrence fits closely the pattern of the double dominant inheritance and does not deviate from it statistically.

10. The data on familial prevalence of *acute* N.C.A. are inconclusive; if they fit into any genetic pattern they suggest a double- or triple-gene, not a simple single-gene, mechanism.

11. Simple imitation, i.e. copying, could not explain the high familial prevalence of the disorder.

12. Feeling ill and having other symptoms did not cause convalescent control subjects to describe symptoms of N.C.A. in relatives.

13. Affected cases are distributed within sibships in random fashion. This is consistent with the assumption of a hereditary disorder.

14. The word "constitutional" and the concepts apparently contained in it are so vague and conflicting as to render them useless.

15. The data while consistent with the supposition of hereditary transmission of the disorder, do not exclude the possibility of some household or other environmental factor or factors, or an interaction of genetic and non-genetic factors.

16. Further appropriate observation and not more speculation is necessary to answer the unsolved problems in this field.

REFERENCES

1. COHEN, M. E., JOHNSON, R. E., *et al.* 1946. A study of neurocirculatory asthenia, anxiety neurosis, and effort syndrome. Final report to the Committee on Medical Research of the Office of Scientific Research and Development under Contract OEMcmr-157. Pp. 135.
2. HILL, A. B. 1948. *Principles of Medical Statistics.* London: Lancet, Ltd.
3. PEARL, R. 1940. *Introduction to Medical Biometry and Statistics.* Philadelphia and London: W. B. Saunders Co.
4. PEARSON, K. 1914. *On the Handicapping of the First-born.* London and Edinburgh: Cambridge Univ. Press.
5. HOGBEN, L. 1934. The analysis of pedigrees. In *The Chances of Morbid Inheritance,* edited by C. P. Blacker. Baltimore: Wm. Wood & Co.
6. WORCESTER, J. Personal communication.
7. HOGBEN, L. 1932*a*. *J. Genet.*, Cambr. 25: 97–112.
8. HOGBEN, L. 1932*b*. *J. Genet.*, Cambr. 25: 211–240.
9. HOGBEN, L. 1932*c*. *J. Genet.*, Cambr. 26: 75–79.
10. HOGBEN, L. 1946. *An Introduction to Mathematical Genetics.* New York: W. W. Norton & Co.
11. STRANDSKOV, H. H. 1942. *Am. Natur.* 76: 156–164.
12. COHEN, M. E., JOHNSON, R. E., & WHITE, P. D. 1948. *Arch. Int. M.* 81: 260–281.
13. WHITE, P. D., COBB, S., *et al.* 1944. *Tr. Ass. Am. Physicians,* 58: 129–137.
14. COHEN, M. E., CONSOLAZIO, F. C., & JOHNSON, R. E. 1947. *J. Clin. Invest.* 26: 339–342.
15. CHAPMAN, W. P., COHEN, M. E., & COBB, S. 1946. *J. Clin. Invest.* 25: 890–896.
16. COHEN, M. E., & WHITE, P. D. 1947. *J. Clin. Invest.* 26: 520–529.
17. WHEELER, E. O., WHITE, P. D., *et al.* 1947–1948. *Proc. N. E. Heart Ass.* pp. 65–66.
18. WHEELER, E. O., WHITE, P. D., *et al.*, 1948. *J. Clin. Invest.* 27: 562.
19. BEARD, G. M. 1869. *Boston M. & S. J.* n.s. 3: 217–221.
20. DA COSTA, J. M. 1871. *Am. J. M. Sc.* 61: 17–52.
21. FREUD, S. 1895. *Neur. Zbl.* 14: 50–66.
22. SAVILL, T. 1899. *Clinical Lectures on Neurasthenia.* New York: Wm. Wood & Co.
23. HARTENBERG, P. 1902. *La Névrose d'Angoisse, Étude Historique et Critique.* Paris: Ancienne Librairie Germer Baillière et Cie., Félix Alcan, éditeur.

24. SAVILL, T. 1907. *Clinical Lectures on Neurasthenia.* New York: Wm. Wood & Co.
25. BALLET, G. 1909. *Neurasthenia.* New York: Wm. Wood & Co.
26. HECKEL, F. 1917. *La Névrose d'Angoisse et les États d'Émotivité Anxieuse.* Paris: Masson et Cie, Éditeurs, Libraires de l'Acad. de Méd.
27. LEWIS, T. 1918. *The Soldier's Heart and the Effort Syndrome.* (First edition). London: Shaw & Sons; New York: Paul B. Hoeber.
28. OPPENHEIMER, B. S., LEVINE, S. A., MORISON, R. A., ROTHSCHILD, M. A., ST. LAWRENCE, W., & WILSON, F. N. 1918. *Mil. Surgeon,* 42: 409–426. [*Note:* Through error this paper appeared under the authorship of Sir Thomas Lewis; cf. editorial note on p. 711 of the same volume of this journal.]
29. OPPENHEIMER, B. S., & ROTHSCHILD, M. A. 1918. *J. Am. M. Ass.* 70(2): 1919–1922.
30. ROBEY, W. H., & BOAS, E. P. 1918. *J. Am. M. Ass.* 71: 525–529.
31. MYERSON, A. 1925. *The Inheritance of Mental Disease.* Baltimore: Williams & Wilkins Co.
32. LEWIS, T. 1940. *The Soldier's Heart and the Effort Syndrome.* London: Shaw & Sons.
33. WOOD, P. 1941. *Brit. M. J.* 1: 767–772; 1: 805–811; 1: 845–851.
34. BROWN, F. W. 1942. *Proc. R. Soc. M.*, Lond. 35: 785–790.
35. SLATER, E. 1943. *J. Neur. Psychiat.*, Lond. 6: 1–16.
36. SHELDON, W. H. 1940. *The Varieties of Human Physique: An Introduction to Constitutional Psychology.* New York & London: Harper & Bros.
37. DRAPER, G., DUPERTUIS, C. W., CAUGHEY, J. L. 1944. *Human Constitution in Clinical Medicine.* New York & London: Paul B. Hoeber, Inc.
38. WERTHEIMER, F. I., & HESKETH, F. E. 1926. *Significance of Physical Constitution in Mental Disease.* Medicine Monographs, Vol. X. Baltimore: Williams & Wilkins Co.
39. PEARL, R. 1933. *Constitution and Health.* London: Kegan Paul, Trench, Trubner & Co.
40. GÜNTHER, H. 1929–1931. *Würzb. Abh. Med.* 26: 155–177.
41. ROTH, W. F., & LUTON, F. H. 1943. *Am. J. Psychiat.* 99: 662–675.
42. GROSS, W. M. 1948. *Eugen. Rev.*, Lond. 40: 140–148.
43. IRVINE-JONES, E. 1933. *Am. J. Dis. Child.* 45: 1184–1195.
44. CRAIG, H. R., & WHITE, P. D. 1934. *Arch. Int. M.* 53: 633–648.
45. LEVIT, S. G. 1936. *J. Genet.*, Cambr. 33: 411–435.
46. DUNN, W. H. 1942. *Psychosomat. M.* 4: 333–354.
47. HARTSHORNE, H. 1864. *Am. J. M. Sc.* 48: 89–92.
48. MACLEAN, W. C. 1867. *Brit. M. J.* 1: 161–164.
49. BEARD, G. M. 1880. *A Practical Treatise on Nervous Exhaustion (Neurasthenia).* New York: Wm. Wood & Co.
50. FLINT, A. 1884. *A Treatise on the Principles and Practice of Medicine.* Nervous Asthenia. Neurasthenia. Philadelphia: H. C. Leabrand Sons Co. Pp. 778.
51. COBB, I. G. 1915. *Practitioner*, Lond. 95: 224–244.
52. LEWIS, T. 1917. Report upon soldiers rated as cases of Disordered Action of the Heart (D.A.H.) or Valvular Disease of the Heart (V.D.H.). Special Report No. 8, Medical Research Committee, Great Britain.
53. FREUD, S. 1920. *Selected Papers on Hysteria and Other Psychoneuroses.* New York & Washington: Nervous and Mental Disease Publishing Co.
54. REICH, W. 1926. *Internat. Zschr. Psychoanal.*, Wien, 12: 25–39.
55. DEUTSCH, H. 1930. Psychoanalyse der Neurosen.
56. ARCHARD, H. J. 1934. *Med. Rec.* 139: 639–641.
57. FENICHEL, O. 1934. *Outline of Clinical Psychoanalysis.* New York: W. W. Norton & Co.
58. THAMES, E. 1935. *J. M. Ass. Alabama,* 5: 54–63.

59. HALDANE, J. B. S., & PRIESTLEY, J. G. 1935. *Respiration.* New Haven: Yale Univ. Press.
60. FREUD, S. 1935. *Autobiography.* New York: W. W. Norton & Co.
61. JOHNSON, O. 1936. *N. England J. M.* 215: 438–443.
62. MARSHALL, W., & TARWATER, J. S. 1938. *J. Nerv. Ment. Dis.* 88: 36–41.
63. SOLEY, M. H., & SCHOCK, N. W. 1938. *Am. J. M. Sc.* 196(6): 840–851.
64. CRILE, G. 1940. *Mil. Surgeon.* 87: 509–511.
65. BAACH, M. 1940. *Deut. Militärarzt,* 10: 405–409.
66. PARKINSON, J. 1941. *Brit. M. J.* 1: 545–549.
67. STARR, I. 1942. *Am. J. M. Sc.* 204: 573–581.
68. MOSCHOWITZ, E., & BERNSTEIN, S. S. 1944. *Am. Heart J.* 28: 177–198.
69. GREENE, R. 1944. *Lancet,* Lond. 2: 307–308.
70. MASTER, A. M. 1944.
71. STRONG, G. F. 1946. *Canad. M. Ass. J.* 55: 344–348.
72. Nomenclature of Psychiatric Disorders and Reactions. Veterans Administration Technical Bulletin 10A-78, October 1, 1947. Washington, D. C.
73. GATES, R. R. 1946. *Human Genetics.* Vols. 1 & 2. New York: Macmillan Co.
74. ROBERTS, J. A. F. 1940. *An Introduction to Medical Genetics.* London: Oxford Univ. Press.

Heredity, Maternal Age, and Birth Order in the Etiology of Celiac Disease[1]

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INTRODUCTION

SINCE Samuel Gee first described celiac disease in 1888, the problem of its etiology has received the attention of many workers. Through clinical, laboratory, and post-mortem studies it has become clear that the underlying fault in celiac disease is a change of a physico-chemical nature in the absorptive mechanism of the intestine (Parsons, 1932), probably a defect in the phosphorylation process in the intestinal mucosa (May *et al.*, 1942). Various factors have been postulated as a cause of this defect; e.g., impaired mechanical function (May & McCreary, 1941), vitamin deficiency (May *et al.*, 1942; Brody & Gore, 1946; Dalton *et al.*, 1946), gastrointestinal allergy (Riley, 1939; Kunstadter, 1942; McKhann *et al.*, 1943), and infection (Brown *et al.*, 1925; Parsons, 1932; O'Donovan *et al.*, 1942).

Constitutional factors in the etiology of celiac disease have been suggested by a number of workers. Stolte (1917) drew attention to the advanced maternal age and the long interval preceding the birth of the affected child (the latter now considered to be an indication of reduced fertility). The tendency for the condition to run in families has been noted by a number of investigators (table 1). Andersen (1947) states as her view that celiac disease develops under adverse circumstances in patients who have an *underlying constitutional defect.*

The present report outlines evidence to indicate that the "underlying constitutional defect" in celiac children is a genetical susceptibility to celiac disease, and that one of the adverse conditions favoring its development is an unfavorable uterine environment, as shown by the late maternal age and late birth rank of these children.

METHODS

The present study formed part of a medical and genetical investigation of celiac disease which was undertaken jointly by the Department of Pediatrics and the Department of Zoology, University of Toronto. The findings of the clinical survey will be reported elsewhere by Ebbs, Stein, and Marriott, and the reader is referred to their paper for an account of the criteria used for the

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TABLE 1. FAMILIAL CASES OF CELIAC DISEASE REPORTED IN THE LITERATURE

AUTHOR	DATE	RELATIONSHIP	NUMBER OF CASES
Hablützel-Weber	1923	Twins	2
Lehndorff & Mautner	1927	Cousins	
		Nephews	
Sauer	1927	Cousins (2 pairs)	4
		Twins	2
Fanconi	1928	Twins	2
		Sibs	2
		Parents or sibs	6
		Consanguineous parentage	1
Haas	1932	Sibs	4
		First cousins (5 pairs)	10
		Second cousins (2 pairs)	4
		Twins	4
		Uncle	1
Feer	Cited by Haas, 1932	Sibs	2
Hess	Cited by Haas, 1932	Sibs	
Thaysen	1935	Sibs (2 pairs)	4
Weller	1939	Sibs	3
		Offspring	2
Collishaw	1940	Twins	2
Rewell	1944	Sibs	2
Davidson & Fountain	1950	"Relatives"	12

diagnosis of celiac disease. The genetical problem was undertaken by the author under the direction of Dr. Norma Ford Walker.

Of the 119 cases of celiac disease which form the basis of this report, 65 have been in-patients at the Hospital for Sick Children, Toronto, and are included in the series used for the clinical report referred to above. In the remaining 54 cases, the diagnosis has been made by a pediatrician of Toronto, Hamilton, or London, Ontario. Selection of the cases to be used was made solely on the basis of accessibility, and willingness of the parents to coöperate (as it was necessary to visit the home of each patient). In particular, cases of fibrocystic disease of the pancreas have been excluded from the series.

For each celiac child whose case formed part of this study, a record of his family history was obtained from his parents. These records included information regarding maternal age at birth and order of birth for each patient and all sibs; the reproductive history of the mother, including miscarriages and stillbirths; and data regarding grandparents, parents and sibs of the patients, with special reference to the appearance of morbid conditions, and particularly of celiac disease, digestive difficulties of any kind, and diabetes mellitus. Diabetes became a special subject of inquiry when it appeared early in the investigation that the incidence of this condition was increased in the celiac patients and their kinships. In some cases the pedigrees were enlarged to include conditions of interest in more distant relatives. We have, in all, 119

cases of celiac disease comprising 104 sibships. There are 109 non-celiac sibs, 208 parents, and 416 grandparents. Of these, information has been obtained for all sibs (of whom seven are unclassified as to celiac disease because they were under six months of age at the time of study), 189 parents, and 361 grandparents.

MATERNAL AGE AND ORDER OF BIRTH IN CELIACS

Maternal age and/or birth rank as factors affecting the uterine environment are known to be of significance in the production of certain diseases in man. An example of this is mongoloid imbecility, where the advanced age of the

TABLE 2. COMPARISON OF MATERNAL AGE AT BIRTH FOR 109 CELIACS AND 91 NON-CELIAC SIBS

MOTHERS OF:	MEAN AGE	STANDARD DEVIATION	NUMBER
(i) Celiacs	30.25	4.604	109
(ii) Non-celiacs	28.20	5.036	91

TABLE 3. ORDER OF BIRTH IN 115 CELIAC CHILDREN

SIZE OF SIBSHIP, s	BIRTH RANK, r								TOTAL N_s	NO. EXPECTED AT EACH RANK N_s/s	NO. EXPECTED AT LATER RANKS	NO. OBSERVED AT LATER RANKS
	1	2	3	4	5	6	7	8				
1	22	—	—	—	—	—	—	—	22	22.00	—	—
2	18	21	—	—	—	—	—	—	39	19.50	19.50	21
3	4	7	16	—	—	—	—	—	27	9.00	9.00	16
4	3	3	5	6	—	—	—	—	17	4.25	8.50	11
5	0	0	0	1	1	—	—	—	2	0.40	0.80	2
6	0	0	0	1	1	3	—	—	5	0.83	2.50	5
7	0	0	0	0	0	1	0	—	1	0.14	0.43	1
8	0	0	0	0	0	0	2	0	2	0.25	1.00	2
Totals									115	—	41.73	58

$\chi^2 = 9.95$, D.F. = 1, $P < 0.01$

mother has been shown by Penrose (1934*a*) to be a causal factor. The relative effects of these two factors are difficult to separate, and in the present study no attempt has been made to do so.

Maternal Age. The maternal age at the birth of the celiac children here studied was significantly later than that of their non-celiac sibs (table 2).

The difference between the mean maternal ages is 2.05 years, and the standard error of this difference is ±0.688 years. The difference is almost three times its standard error, which is statistically significant.

Birth Order. The birth rank for celiacs is significantly later than for their non-celiac sibs (table 3). The figures for the number of patients expected at the later birth ranks include half of those sibships of size two, one-third of those of size three, one-half of those of size four, two-fifths of those of size

five, etc. These are compared directly with the number of patients observed in the same ranks.

The evidence that maternal age and birth rank are both significantly late in celiac children suggests that the unfavorable uterine environment provided by the older or multiparous mother may be effective in bringing about the manifestation of celiac disease. It is possible, of course, that the finding of late birth rank in these children reflects family limitation by those parents who have previously borne a celiac child. The part which might be played by such voluntary family limitation is extremely difficult to assay, particularly since celiac disease normally manifests itself, not at birth, but at nine months of age or even later.

GENETIC CONSTITUTION OF CELIAC CHILDREN

Although there has been no previous published study of the genetics of celiac disease, there exists a general impression among physicians that the disease tends to run in families. This general impression is borne out by the number of recorded cases of the condition occurring in more than one member of the family (table 1).

Celiac Disease in Sibships

Penrose (1934*b*) has given a method for calculating the expected random proportions of sibships with more than one member affected, given the approximate incidence of the condition and the approximate mean family size. The incidence of celiac disease in Toronto children is estimated by Dr. J. H. Ebbs as between 1/100 and 1/1000. For this test, a mean sibship size of 3 has been used, though the actual mean sibship size in our series is somewhat lower. This method has been used to calculate the expected numbers of sibships with 1, 2, and 3 members affected, which are compared below with the observed (table 4).

The number of sibships in which more than one member is affected markedly exceeds the expected random distribution. This observation suggests that genetic factors operate in the etiology of celiac disease, though this test alone does not rule out the possibility of environmental factors such as infection.

Proportions of Affected Relatives

A history of celiac disease during early childhood was elicited in 13% of the sibs of our celiac series, 6% of their parents, and 1% of their grandparents (table 5).

Because of the relatively short time during which celiac disease has been recognized, no great accuracy is claimed for the findings with respect to incidence of celiac disease in parents and grandparents of affected children. In 10 of the 11 cases of affected parents, the diagnosis of celiac disease was made

not at the time, but later, when the same symptoms appeared in the offspring. In the eleventh case, the diagnosis was made at the time by the patient's father, a physician. For two of the four grandparents regarded as affected, disturbance of fat digestion has persisted to adult life. The remaining two grandparents suffer from tropical sprue, a disease which appears to be a manifestation of the same morbid condition as celiac disease (Hanes & McBryde, 1936).

TABLE 4

NUMBER OF AFFECTED SIBS	NUMBER OF SIBSHIPS EXPECTED (IF INCIDENCE 1/100)	NUMBER OF SIBSHIPS EXPECTED (IF INCIDENCE 1/1000)	NUMBER OF SIBSHIPS OBSERVED
1	102.96	103.90	92
2	1.04	0.10	9
3	0.00	0.00	3
Totals	104.00	104.00	104

TABLE 5. THE INCIDENCE OF CELIAC DISEASE AMONG RELATIVES OF CELIAC PATIENTS

RELATIONSHIP	TOTAL NUMBER*	NUMBER AFFECTED	INCIDENCE
Propositi	104	104	1.00
Sibs	117	15	0.13
Parents			
Total	189	11	0.06
Fathers	94	8	0.09
Mothers	95	3	0.03
Grandparents			
Total	361	4	0.01
Paternal	182	2	0.01
Maternal	179	2	0.01

*i.e., total number for which information is available.

The Association of Diabetes Mellitus and Celiac Disease

A noteworthy finding in the present study has been the high incidence of diabetes in the celiac patients and their relatives. A diabetic family history was reported in 36 (35%) of our 104 celiac sibships. This figure may be compared with those of Wilkerson and Krall (1947), who report that 38.6% of their diabetic group and only 18.4% of their non-diabetic group have one or more diabetic relatives.

In table 6, the incidence of diabetes among the celiacs, their sibs, parents, and grandparents is compared with the incidence in similar age groups in the general population, the latter as calculated by Joslin *et al.* (1946) from figures of the United States National Health Survey of 1936–37. (Dr. A. L. Chute has estimated that the incidence of diabetes in children under 15 years of age in Toronto is 0.0005, a value close to Joslin's figure of 0.0004.)

No sib, parent, or grandparent listed in table 5 as celiac is listed in table 6 as diabetic; in other words, the occurrence of celiac disease and diabetes in the same individual has been observed only in two celiac propositi. Although the observation of two diabetics among 119 celiac patients seems at first glance to be hardly worthy of note, the probability of observing two or more diabetics among 119 children, by chance alone, is less than 1 in 100.

Table 6 shows that the incidence of diabetes in the celiac patients and their relatives is markedly higher than in the general population at comparable ages, according to the National Health Survey prevalence figures. It is possible that the difference depends, at least in part, upon an underestimate of the prevalence of diabetes; indeed, the findings of the Oxford Survey (Wilkerson & Krall, *loc. cit.*) suggest that the true prevalence may be higher than the

TABLE 6. INCIDENCE OF DIABETES IN CELIACS AND THEIR RELATIVES

RELATIONSHIP	MEAN AGE (YRS.) AT TIME OF STUDY (APPROX.)	TOTAL NUMBER	NO. DIABETICS OBSERVED	INCIDENCE IN CELIAC SERIES	INCIDENCE IN POPULATION	NO. DIABETICS EXPECTED
Celiacs	5	119	2	0.017	0.0004	0.05
Sibs	8	102	2	0.020	0.0004	0.04
Parents	37	189	1 (+1 potential diabetic)	0.005	0.0026	0.49
Grandparents	63	361	20	0.055	0.0143	5.16
Totals	—	771	25	—	—	5.74

$\chi^2 = 65.11$, D.F. = 1, $P < 0.001$

National Health Survey estimate. The Oxford Survey figures are not suitable for comparison with the present series, because they include a large proportion (30 of the total of 70, or 42.9%) of "new" cases, i.e., cases which were previously unknown but were diagnosed in the course of the survey, whereas our figures deal only with known diabetics. In the absence of recent, reliable figures for the prevalence of diabetes in the general population, it must be concluded that an association between diabetes mellitus and celiac disease is suggested, though not proven, by our data. It is hoped that further studies in other centers will serve either to establish or to disprove the suggested association.

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SUMMARY

Some constitutional factors in the etiology of celiac disease have been investigated.

The observations that celiacs are born at later maternal ages and at later birth ranks than their non-celiac sibs suggest that disturbance of prenatal growth brought about by the unfavorable uterine environment provided by the older or multiparous mother may be a factor in the production of celiac disease.

Heredity as an etiological factor is suggested by the number of instances of the condition in more than one member of a family which have been recorded in the literature and observed in the present study.

Analysis of the frequency of affected sibs has shown that celiac disease appears in more than one member of a sibship far more frequently than is to be expected if its distribution depends upon chance alone.

The incidence of diabetes mellitus among the celiacs here studied and their relatives is higher than its reported incidence in the general population. This suggests a possible association between the two conditions.

REFERENCES

ANDERSEN D. H. 1947. The relationship of celiac disease, starch intolerance, and steatorrhea. *J. Pediat.*, S. Louis, 30: 564–582.

BRODY, H. P. & GORE, L. 1946. Celiac disease and folic acid. *Lancet*, Lond. 2(251): 618.

BROWN, A., COURTNEY, A. M., DAVIES, G. A., & MACLACHLAN, I. F. 1925. The etiology of chronic intestinal indigestion. *Am. J. Dis. Child.* 30: 603–631.

CHUTE, A. L. Personal communication.

COLLISHAW, D. 1940. Celiac disease in twins. *Brit. M. J.* 2: 904.

DALTON, H. W., THOMSEN, M. L., & WILSON, V. K. 1946. Celiac disease and folic acid. *Lancet*, Lond. 2(251): 652.

DAVIDSON, L. S. P., & FOUNTAIN, J. R. 1950. Incidence of the sprue syndrome. *Brit. M. J.* 1: 1157–1161.

EBBS, J. H. Personal communication.

EBBS, J. H., STEIN, W., & MARRIOTT, M. J. Unpublished.

FANCONI, G. 1928. Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungsstörung. *Jahrb. Kinderh., Abh. Kinderh.*, 21.

GEE, S. 1888. On the celiac affection. *S. Barth. Hosp. Rep.*, Lond. 24: 17–26.

HAAS, S. V. 1932. Celiac disease: its specific treatment and cure without nutritional relapse. *J. Am. M. Ass.* 99: 448–452.

HABLÜTZEL-WEBER, E. 1923. *Über intestinalen Infantilismus und das Schicksal der Träger desselben.* Zürich: Leemann & Co.

HANES, F. M., & MCBRYDE, A. 1936. The identity of sprue, non-tropical sprue, and celiac disease. *Arch Int. M.* 58: 1–16.

JOSLIN, E. P. ROOT, H. F., WHITE, P., MARBLE, A., & BAILEY, C. C. 1946. *The Treatment of Diabetes Mellitus*, 8th Ed. Philadelphia: Lea. Pp. i, 33.

KUNSTADTER, R. H. 1942. Gastrointestinal allergy and the celiac syndrome. *J. Pediat.*, S. Louis, 21: 193–197.

LEHNDORFF, H., & MAUTNER, H. 1927. Die Coeliakie. *Erg. inn. Med. Kinderh.* 31: 456-593.

MAY, C. D., & MCCREARY, J. F. 1941. The absorption of vitamin A in celiac disease. *J. Pediat.*, S. Louis, 18: 200–209.

MAY, C. D., MCCREARY, J. F., & BLACKFAN, K. D. 1942. Notes concerning the cause and treatment of celiac disease. *J. Pediat.*, S. Louis, 21: 289–305.

MCKHANN, C. F., SPECTOR, S., & MESERVE, E. R. 1943. An associaion of gastrointestinal allergy with celiac syndrome. *J. Pediat.*, S. Louis, 22: 362–372.

O'DONOVAN, D. K., MCGRATH, J., & BOLAND, S. J. 1942. Giardial infestation with steatorrhea. *Lancet*, Lond. 2(243): 4–6.

PARSONS, L. G. 1932. Celiac disease. *Am. J. Dis. Child.* 43: 1293–1346.

PENROSE, L. S. 1934*a*. A method of separating the relative etiological effects of birth order and maternal age, with special reference to mongolian imbecility. *Ann. Eugen.*, Cambr. 6: 108–127.

PENROSE, L. S. 1934*b*. *The Influence of Heredity on Disease.* London; Lewis. Pp. iv + 78.

REWELL, R. E. 1944. Case of sprue syndrome of unusual etiology. *Guy's Hosp. Rep.*, Lond. 93: 74–78.

RILEY, I. D. 1939. Metabolic eczema in idiopathic steatorrhea. *Lancet*, Lond. 1(236): 262–264.

SAUER, L. W. 1927. Celiac disease; etiology, prognosis, and standardization of treatment. *Am. J. Dis. Child.* 34: 934–949.

STOLTE, K. 1917. Schwere Durchfälle bei neuropathischen Kindern. *Jahrb. Kinderh.* 36: 89–127.

THAYSEN, T. E. H. 1935. Ten cases of idiopathic steatorrhea. *Q. J. Med.*, Oxf. 4: 359–395.

THOMPSON, M. W. 1947. *Some Etiological Factors in Celiac Disease.* Ph.D. Thesis, University of Toronto. Unpublished.

WELLER, G. L. 1939. The early diagnosis of non-tropical sprue, with a note on its familial incidence. *Am. J. Digest. Dis.* 5: 254–257.

WILKERSON, H. L. C., & KRALL, L. P. 1947. Diabetes in a New England town. *J. Am. M. Ass.* 135: 209–216.

A Genetic and Clinical Study of Intestinal Polyposis, a Predisposing Factor for Carcinoma of the Colon and Rectum[1]

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IN a recent paper (Gardner & Stephens, 1950) a pedigree was presented in which a high incidence of carcinoma of the lower digestive tract was represented. Nine deaths out of a total of twelve adult deaths in one branch of the kindred were attributed directly or indirectly to this disease. These included the wife in the original couple (*II-7*, fig. 2, Gardner & Stephens, 1950), her four children, and four of her grandchildren. Although the details of the family history of the woman were not complete, evidence was presented to indicate that some cases of carcinoma of the digestive tract had occurred among her relatives. No evidence of carcinoma was found in the family of her husband. This suggested an hereditary pattern coming through the line of the mother to the members of her immediate family and their descendants. A dominant type of inheritance was indicated.

While the report of this group was being prepared for publication, a grandson (*IV-219*, fig. 2, Gardner & Stephens) of the woman was found to have multiple polyposis of the colon. For several years he had observed symptoms similar to those of his brothers and cousins who had died with carcinoma of the rectum and colon. The symptoms, particularly the bleeding from the rectum, had become progressively more severe. Being well aware of the condition in other members of his family, this young man sought medical attention. His family doctor discovered multiple polyposis in the colon and referred him to a specialist. He was treated surgically and recovered satisfactorily from the operation.

Multiple polyposis is known to be a predisposing factor for carcinoma. This confirmed case in a member of the family group, and other evidence obtained from the family studies and medical records, led to the suspicion that multiple polyposis was the factor responsible for the high incidence of carcinoma of the colon and rectum in this group. To determine whether or not the disease

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was continued in an hereditary pattern in other members of the family group, a clinic for the detection of multiple polyposis and carcinoma of the colon and rectum was established in connection with the Division of Oncology at the Salt Lake General Hospital. Nearly all of the living members of the family group over 5 years of age were examined. The objective of the present paper is to report and interpret the results of these examinations. Evidence is presented to show that multiple polyposis follows an hereditary pattern and predisposes to carcinoma in the family group under consideration. The study also demonstrates a practical application for the principles of heredity in medical practice.

HISTORICAL

For many years single polyps have been known to occur rather commonly in the colon. Some investigators have found that 5–10% of the general population have such polyps. The uncommon condition of multiple polyps or polyposis has been described by several investigators. The literature was reviewed by Dukes (1930), Hoxworth and Slaughter (1948) and others. The tendency for the disease to occur in certain family groups more frequently than in the general population was recognized by early students of the problem. Only references dealing with the hereditary aspects of the disease are cited here.

According to Dukes (1930), polyposis of the colon was first recognized as a familial and potentially malignant condition by W. Harrison Cripps in 1882. Since the recognition and description by Cripps, cases have been reported by a large number of investigators. Niemack (1902) reported two cases in related individuals and suggested the hereditary nature of the disease. Dukes (1925–26) described at length the stages of polyposis of the large intestine and discussed the relationship of the condition with cancer. Hullsiek (1928) listed from the literature 127 cases of multiple polyposis of the colon and tabulated data concerning age of patients, duration of illness, site of polyps, malignancy, treatment, and cause of death. The cause of death was often carcinoma. Relatives with the same disease were also listed.

The hereditary nature of polyposis was emphasized in the review by Dukes (1930). Dukes cited pedigrees previously presented by Cripps, Niemack, Zahlmann, Hertz, Mueller, Lockhart-Mummery, Jüngling, and others and included an extensive bibliography. McKenney (1936) also emphasized the familial nature of multiple polyposis. He presented two family pedigrees.

More recent reports and discussions by Lockhart-Mummery (1934) and Lockhart-Mummery and Dukes (1939) identified the average age for the appearance of the polyps at about 20 years. The youngest of 20 patients was 7 years of age, and the oldest was 43. The average age of death from carcinoma following polyposis was about 20 years younger than was the average age of death from carcinoma of the rectum and colon in the general population. These authors presented 10 family pedigrees showing polyposis and cancer of the rectum and colon.

Falk (1942) described a family in which six of seven children had multiple polyps. Two of the six died with carcinoma. Pfeiffer and Patterson (1945) reported on five polyposis patients, four of whom had a family history of polyposis. Estes (1948) collected 355 cases of polyposis from the literature. He reported on a family in which the mother and six of her children were found to have polyposis. C. M. Gardner (1948) found the condition to be primarily a disease of young adults. He showed that multiple polyposis usually appears between puberty and 30 years of age.

Several of the pedigrees cited above illustrate the pattern of simple dominant inheritance. A recent report by Boehme (1950) was based on his study of seven related individuals with multiple polyposis. A family history covering a period of 136 years was included. The hereditary pattern of a simple dominant factor was demonstrated and followed through several successive generations.

METHODS

The family histories were obtained through personal interviews with members of the group. As a part of each interview, places of residence and names of doctors and hospitals were carefully noted. These leads were followed up as completely as possible. Death certificates for those people no longer living were reviewed. The leads obtained from this source concerning pathological findings from operations and autopsy reports were traced to their source and original records were examined wherever possible.

A clinic[2] for the examination of living members of the group was established at the Salt Lake General Hospital. The routine examinations included a sigmoidoscopy, hematocrit, and guaiac test. A more detailed family history than the one obtained at the home of the person was secured at the hospital. Individuals showing positive results for either the sigmoidoscopy or guaiac test, and those having a history of digestive disturbance and bleeding from the rectum, were examined further by means of air contrast barium enema.

In a few cases where the distance was too great to bring the people to Salt Lake City, the cooperation of private physicians was solicited to make the examinations. Some members of the group were already under the care of a private physician. The data for these were obtained from their doctors. Reports of all examinations at the clinic were sent to the family physicians of the people concerned.

EXPERIMENTAL RESULTS

History of People Not Living

The members of the family group under consideration (Kindred 109 in the records of the Laboratory of Human Genetics, University of Utah) are symbolized in the accompanying pedigree chart (fig. 1). A diagramatic representation of the entire kindred and a description of this group with reference to the incidence of carcinoma of the colon and rectum was presented previously (Gardner & Stephens, 1950). Further evidence from the family histories and additional medical and autopsy records located since the previous publication has substantiated the contention that the mother (*I-2*, fig. 1) and three of her

[2] The clinic was supervised by Dr. E. J. Eichwald, of the Division of Oncology. Dr. William Erickson performed the sigmoidoscopic examinations, Dr. Marshall Landa did the barium enema examinations, Michico Hattori performed the guaiac and hematocrit tests, and Dr. E. J. Eichwald made the pathological studies. Martha Beal recorded the case histories in the hospital.

FIG. 1. Pedigree of family group showing incidence of polyposis and carcinoma of the digestive tract.

children (*II-1*, *II-2*, and *II-3*) died with carcinoma of the lower digestive tract. A large number of relatives of her husband (*I-1*) are now known, in addition to those represented previously (Gardner & Stephens, 1950, fig. 2, Family B). No cancer has been detected in this group.

Greater uncertainty has arisen concerning the condition of *II-4*. He was reported previously to have undergone surgery for carcinoma and died shortly thereafter in an accident. Every possible source of direct information available at present has been explored and no conclusive evidence has been located to indicate whether or not he had carcinoma or polyposis of the colon at the time of his death. New evidence has been obtained which supports the previous findings concerning the cause of death of *III-1*, *III-8*, and *III-9*. These three were reported to have died with carcinoma of the rectum and colon.

III-15 was reported in the death certificate to have died with adenocarcinoma of the stomach. The diagnosis of adenocarcinoma of the stomach with metastases, and obstructions of the bowel, was recorded in the hospital records. The roentgenological and fluoroscopic findings at the time of admission to the hospital in his final illness indicated dilated and gas filled loops of the small intestine suggestive of a subacute obstruction of the bowel. The autopsy findings were: Carcinoma of stomach with metastases to mesentery, liver, spleen, abdominal wall and diaphragm. Terminal small bowel obstruction and large bowel obstructions were also reported at autopsy. *III-15* had a history of rectal bleeding for several years before his death.

Among the 13 members of the group who died after reaching maturity, 8 died with carcinoma of the digestive tract, one (*II-4*) may have had polyposis or carcinoma at the time of death, two (*III-5* and *III-11*) met accidental death, one (*III-3*) was reported on the death certificate to have died with "intestinal flu," and one (*IV-11*) died with staphylococcemia while this study was in progress. The colon of *IV-11* was examined at autopsy and no polyps were found. Six members of the family group died in infancy or early childhood.

Results of Examinations for Detection of Polyposis and Carcinoma

All but two of the living members of the family group over five years old have been examined with the sigmoidoscope. The results of the examinations are summarized in table 1. The individuals are identified according to their position on the pedigree chart (fig. 1). The age is given in years at the time of the examination. Sigmoidoscopic findings are given as positive or negative for multiple polyposis. The guaiac test results are also given as positive or negative and are interpreted to indicate the presence or absence of blood in the fecal material at the time of the examination. In some cases an explanation was found at sigmoidoscopy for a positive guaiac test, which obviated the necessity for the barium enema, which otherwise was recommended to follow a positive guaiac test. The results of the hematocrit test are given in terms of percentage of packed red cells in 1 cc. of oxalated whole blood. The barium

TABLE I. RESULTS OF EXAMINATIONS FOR DETECTION OF POLYPOSIS AND CARCINOMA

INDIVIDUAL	AGE	SIGMOIDOSCOPY	GUAIAC	HEMATOCRIT	BARIUM ENEMA	BIOPSY
III-2	45	Positive	Positive	36	Not diagnostic	Malignant
III-4	40	Negative	Positive	49	—	—
III-7	47	Negative	Negative	42	—	—
III-10	40	Not examined	—	—	—	—
III-12	32	Positive	—	—	Not diagnostic	Not malignant
III-13	45	Negative	—	—	Negative	—
III-14	43	Positive	—	—	Positive	Malignant
III-16	39	Negative	Positive	50	Negative	—
III-17	34	Negative	Negative	49	—	—
III-18	34	Negative	—	—	Negative	—
III-19	32	Negative	Negative	42	—	—
IV-1	18	Negative	Positive	44	—	—
IV-3	26	Not examined	—	—	—	—
IV-5	15	Negative	Negative	43	—	—
IV-6	11	Negative	Negative	42	—	—
IV-7	20	Positive	Positive	43	Positive	Not malignant
IV-8	17	Negative	Negative	44	Negative	—
IV-9	13	Negative	Negative	45	—	—
IV-10	18	Negative	Negative	48	—	—
IV-11	20	Not examined	—	40	—	—
IV-12	18	Negative	Positive	48	—	—
IV-13	16	Negative	Positive	44	—	—
IV-16	20	Negative	Negative	46	—	—
IV-17	19	Negative	Negative	—	—	—
IV-18	13	Negative	Negative	43	—	—
IV-19	10	Negative	—	—	—	—
IV-20	6	Negative	—	—	—	—
IV-22	13	Negative	—	—	—	—
IV-23	9	Negative	—	—	—	—
IV-24	19	Negative	Negative	45	—	—
IV-25	14	Negative	Positive	40	Negative	—
IV-26	11	Negative	Negative	43	—	—
IV-27	6	Negative	—	40	—	—
IV-28	2	Not examined	—	—	—	—
IV-29	19	Positive	Positive	48	Not diagnostic	Inadequate
IV-30	14	Negative	Positive	43	Negative	—
IV-31	12	Negative	Positive	40	Negative	—
IV-32	16	Negative	Negative	43	—	—
IV-33	10	Negative	Negative	39	—	—
IV-34	6	Negative	Negative	38	—	—
IV-35	4	Not examined	—	40	—	—
IV-36	8	Negative	Negative	41	—	—
IV-37	6	Negative	Negative	41	—	—
IV-38	4	Not examined	—	—	—	—
IV-39	3	Not examined	—	—	—	—
IV-40	5	Not examined	—	36	—	—
IV-41	2	Not examined	—	—	—	—
V-1	7	Negative	Negative	42	—	—
V-2	5	Not examined	—	—	—	—
V-3	2	Not examined	—	—	—	—
V-4	1	Not examined	—	—	—	—

enema results are given as positive or negative for multiple polyposis. Biopsy results are given as malignant or non-malignant for biopsied polyps, from the pathological report. Thirty-nine of the 50 living members of the group were examined. Five were positive at sigmoidoscopy and 34 were negative. Four of the 5 individuals positive at sigmoidoscopy were successfully biopsied and two of the 4 were found to have carcinoma. Nine of the 11 who were not examined were children under 6 years of age and 2 were adults.

The results for the five positive cases are summarized briefly as follows:

III-2 was found at sigmoidoscopy to have multiple polyposis of the lower colon. The guaiac was positive and the hematocrit of 36% was below the normal range for a man of 45 years of age. A biopsy was taken from two polyps. The pathological report showed one of these polyps to be malignant. There was no evidence of invasion at the stalk. The barium enema examination was not diagnostic. *III-2* had a history of rectal bleeding.

III-12 also had a history of rectal bleeding. His mother died when he was a child and he was cared for by his sister (*III-7*). She reported that he had a good deal of trouble with the lower digestive tract all his life. According to his sister he had serious constipation when he was only two years old and has had frequent difficulty since that time. During the past few years he has noticed a considerable amount of bleeding from the rectum. This became more severe during the eight months preceding the examination. While this study was in progress, he recognized the same symptoms in himself which were present in other members of his family who had died with carcinoma, and sought medical attention. Multiple polyposis of the colon was discovered by his physician and he was referred to a specialist for treatment. The entire colon was removed in a single operation. The patient made a good postoperative recovery.

III-14 observed evidence of bleeding from the rectum over a period of about six years before the polyposis was discovered. The bleeding became severe in the spring of 1949. He sought medical attention at that time but no diagnosis was made. A year later another doctor discovered multiple polyposis in the entire colon and rectum. *III-14* was referred to a specialist immediately, and on July 1, 1950, underwent surgery for the removal of the lower half of the colon. The specimen included one large tumor which had produced a nearly complete obstruction. More than 40 smaller polyps were counted in the excised portion of the colon. On July 11 a second operation removed the rectum and established a colostomy. The remaining part of the colon was removed on September 18. The pathological report showed that several of the polyps which were biopsied had become malignant. No evidence of metastasis was observed.

IV-7 had a history of slight rectal bleeding but was apparently in good health. The sigmoidoscopic examination showed numerous grayish-red polyps in the colon. The guaiac test was positive but the hematocrit result was within the normal range for a female 20 years of age. She was examined fluoroscopically at the time of the barium enema. From both examinations numerous polyps were detected in the rectum and sigmoid colon. The diagnosis of multiple polyposis was established on the basis of these tests. The biopsied polyps were not malignant.

IV-29 was found at sigmoidoscopy to have polyps in the colon. He was in excellent health. The guaiac test was strongly positive but the hematocrit was within the normal range for a male 19 years of age. The biopsy was inadequate for diagnosis. From the barium enema examination, circular defects which could be polyps were indicated in the colon. A second barium enema failed to confirm the findings of the first. *IV-29* left immediately for military duty and was not available for further study.

In addition to the five cases described above one questionable case should be mentioned. *IV-31* gave a strongly positive guaiac from two separate tsts. The hematocrit was probably within the normal range for a female 12 years of age. No polyps could be detected at sigmoidoscopy or barium enema.

Incidence of Surface Tumors in Family Group

Besides the high incidence of polyposis and carcinoma of the lower digestive tract in this family group, another characteristic, apparently hereditary, was observed early in the study. Conspicuous surface lumps or tumors are present on the head and body of several living members of the group. Great variation was observed in the size and superficial nature of the lumps as well as the number present on different individuals. The exact nature and significance of these tumors is not known. As far as it can be determined, all of those who have died with carcinoma of the digestive tract also have had some of these surface tumors. Clear evidence has not been obtained for the two older members of the group (*I-2* and *II-1*, fig. 1) who died with carcinoma of the lower digestive tract. *I-2* died in 1909 and no one has been located who remembers her well enough to be sure whether or not she had surface tumors on her body. *II-1* died in 1935. None of his living relatives can be sure whether or not he had such tumors. As shown in fig. 1 all other members of the group who died with carcinoma and the one (*II-4*) suspected of having polyposis or carcinoma at the time of his death, had surface tumors.

In one case (that of *III-9*, fig. 1) a surface tumor was removed from the jaw region only a few months before the carcinoma was detected in the lower digestive tract. Although the specimen removed was shown not to be malignant, several family members have expressed the feeling that a relationship existed between the two conditions. Some believe that "something stirred up by the previous operation on the jaw" brought on the condition in the digestive tract which proved fatal. This was doubtful, since there was symptomatic evidence for multiple polyposis of the colon for several years before the operation on the face. However, the feeling in the family is strong enough to make difficult the study of these surface tumors. Several members have refused to allow a doctor to make even a superficial examination. Some (*III-2*, for example) have lived with conspicuous tumors for many years because of the fear of having them removed. In some cases a social complex has developed and likely an alteration in personality because of conspicuous tumors.

As shown in fig. 1, all five (*III-2*, *III-12*, *III-14*, *IV-7* and *IV-29*) of the people shown by examination to have multiple polyposis also have surface tumors. The growths on these five people appear much alike but they are more numerous in some than in others. Family group members call this type, "bone tumors" in comparison with other soft, cyst-like tumors which also occur in the group. No critical examination of the nature of the surface tumors has been made. In addition to these five, three younger members of the group

have similar surface tumors. Two (*IV-9* and *IV-20*) of these were shown at sigmoidoscopy to be free from polyposis. The third (*IV-28*) was not examined. The ages of these children were 13, 6 and 2, respectively.

Mode of Inheritance

The pattern (fig. 1) of inheritance of polyposis shown in this group is characteristic of a simple dominant gene. Other studies cited above from the literature have resulted in similar conclusions for the same condition in other family groups. When the present study began the pattern of dominant inheritance was established on the basis of family histories of individuals who died with carcinoma of the digestive tract. An hypothesis was accordingly set up to establish the expected pattern for living members of the group. Predictions were made concerning the probable incidence of polyposis in younger members who had not experienced symptoms of the disease. Results of examinations have verified the hypothesis. It will be observed from the pedigree chart that in every sibship where the trait is expressed, one parent is affected. About half of the children of an affected parent have the disease while all of the children of those parents not affected are normal. Since no two people both of whom have the abnormality are known to have married, the behavior of the gene in homozygous condition is unknown. Presumably all of the matings which have occurred in the family group are of the backcross type ($Pp \times pp$). These data should have practical significance for family members and their doctors in dealing with the problem in the family.

One difficulty comes from a lack of knowledge concerning the time of onset of polyposis in young individuals. There is no agreement among investigators concerning the period in life at which the polyposis first appears. Some students of the problem believe that the polyps first develop in young adults. Others consider it possible that they are present earlier in life, and some have suggested that they may even be present at birth. No specific evidence has been obtained so far on this point but evidence likely will be secured as the study progresses. People of all ages are included in the study. They will be examined periodically over a period of years. The youngest person (*IV-29*) found so far to have polyposis is 19 years of age. If the polyps develop first in young adults it is likely that several younger members of the group, now negative, carry the gene and may be expected to express the trait as they grow older.

The pattern of inheritance for the surface tumors also conforms to that of a simple dominant gene. The incidence is essentially parallel with that of multiple polyposis. The significance of this parallel is not known. It is difficult to visualize any immediate connection between benign surface tumors and polyposis of the lower digestive tract, yet the correlation is impressive and may represent more than a coincidence. Some general gene-controlled process may give rise to both manifestations. If no relationship is established between the two expressions, the possibility of a genetic linkage between two dominant

genes, responsible for the two expressions, still remains to be explored. This latter suggestion would imply that the two genes are located near each other on the same chromosome.

SUMMARY

A pedigree is presented including a total of 68 descendants of one couple. Six died in infancy or early childhood. From a total of 12 adult deaths, 7 have resulted directly from carcinoma of the digestive tract. The mother died with carcinoma of the bowel. Intestinal polyposis was suggested as the predisposing factor for carcinoma. To determine whether or not an hereditary pattern was continued in the younger members of the group, examinations including sigmoidoscopy and barium enema were provided for all living members for the detection of polyposis and carcinoma. From a total of 50 living individuals, 34 were negative and 5 were positive at sigmoidoscopy for polyposis. Two of the five had well established carcinoma. Nine were under 6 years of age and were not examined, and 2 adults were not examined. Surface tumors of unknown nature and significance were also present in all of the living individuals with polyposis or carcinoma. Surface tumors were also present among those who died with carcinoma of the colon and rectum. The pattern of simple dominant inheritance was indicated for both the polyposis and the surface tumors.

REFERENCES

BOEHME, E. J. 1950. The surgical treatment of familial polyposis of the colon. *Ann. Surg.* 131: 519–533.

DUKES, C. 1925–26. Simple tumors of the large intestine and their relation to cancer. *Brit J. Surg.* 13: 720–733.

DUKES, C. 1930. The hereditary factor in polyposis intestini, or multiple adenomata. *Cancer Rev.*, Brist. 5: 241–256.

ESTES, W., JR. 1948. Familial polyposis and carcinoma of the colon. *Ann. Surg.* 127: 1035–1046.

FALK, V. S. 1942. Familial polyposis of the colon. *Arch. Surg.* 45: 123–128.

GARDNER, C. M. 1948. Polyposis of the colon. *Arch. Surg.* 56: 75–78.

GARDNER, E. J., & STEPHENS, F. E. 1950. Cancer of the lower digestive tract in one family group. *Am. J. Human Genet.* 2: 41–48.

HOXWORTH, P. I., & SLAUGHTER, D. P. 1948. Polyposis (adenomatosis) of the colon. *Surgery*, 24: 188–211.

HULLSIEK, H. E. 1928. Multiple polyposis of the colon. *Surg. Gyn. Obst.* 47: 346–356.

LOCKHART-MUMMERY, J. P. 1934. *Diseases of the Rectum and Colon.* Baltimore: Wm. Wood & Co. p. 234.

LOCKHART-MUMMERY, J. P., & DUKES, C. E. 1939. Familial adenomatosis of colon and rectum. *Lancet*, Lond. 237: 586–589.

MCKENNEY, D. C. 1936. Multiple polyposis of colon, familial factor and malignant tendency. *J. Am. M. Ass.* 107: 1871–1876.

NIEMACK, J. 1902. Intestinal polyposis and carcinoma. *Ann. Surg.* 36: 104–108.

PFEIFFER, D. B., & PATTERSON, F. M. S. 1945. Congenital or hereditary polyposis of the colon. *Ann. Surg.* 122: 606–624.

A Case of Neurofibromatosis from Car Nicobar

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DURING the year 1948, in the course of an anthropological survey of the Nicobarese of Car Nicobar island, on behalf of the Department of Anthropology, Government of India, I encountered in the village of Kenyuaka a young man bearing the name of Lazarus, aged about 22, who exhibited numerous surface tumors of a kind characteristic of neurofibromatosis (fig. 1). Further enquiries revealed that Lazarus' mother, Ta-pi-Sang, who was born and married in the same village, was similarly affected. She died about 20 years ago. Lazarus had a normal younger brother who died at the age of 7 years. Ta-pi-Sang had

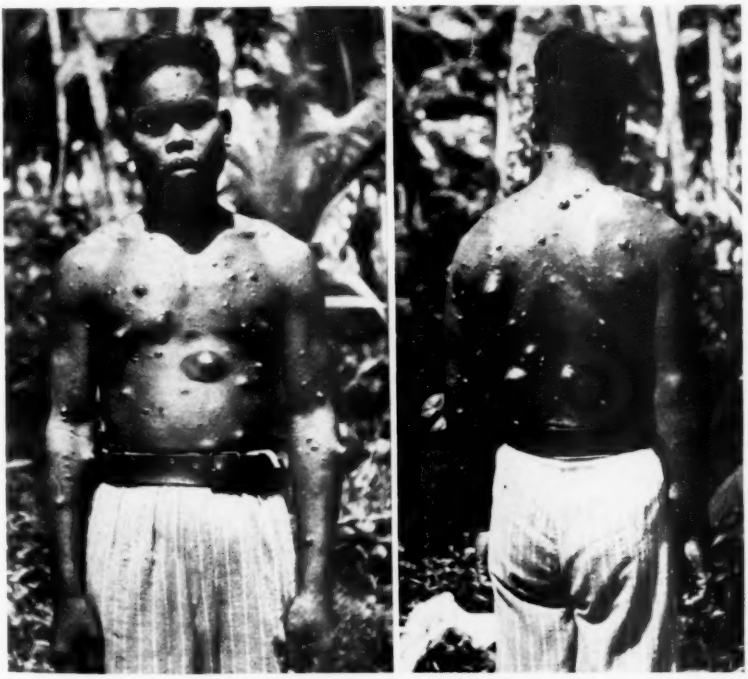

FIG. 1. Neurofibromatosis in a Nicobarese male, Lazarus.

one brother and two sisters, all of whom were normal and had normal children; none of these relatives, however, is now living. Lazarus himself was unmarried at the time of my last enquiry in October, 1950.

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From the letters of Canon John Richardson, a Nicobarese himself and the head of the S.P.G. Mission, Car Nicobar, the foremost living authority on the Nicobarese and a well-informed man, it appears that Ta-pi-Sang's neurofibromatosis was the first of its kind in the island. There is no local tradition associated with this disease, although it goes by the native name of "Mi-long," which means a tumor. Car Nicobar (9° N. lat., 93° E. long.) is 49 square miles in area and has a population of 8726 (♂4378, ♀4348) according to a census carried out by the local government during 1945–46, after the Japanese surrender. There are 15 villages in the island, but in none of them did I find a single additional case of neurofibromatosis.

Lenz (cited by Grohmann, 1939) is of the opinion that somatic mutations are possibly responsible for the tumors in neurofibromatosis and that they are not the regular expression of a pathological gene. Ta-pi-Sang's neurofibromatosis may be an example of such a somatic mutation. But as the disorder appeared in mother and son, and not in previous generations, it is probably to be regarded as a dominant germinal mutation. In an extended account of this disease, Gates (1946) points out that it is known in Europeans, Chinese, Japanese, Tamils, Burmese and Negroes, that it is generally dominant in inheritance, and that it appears to occur frequently as a mutation.

These mutations die out among the aborigines, as such people always find it difficult to get a mate. I have a large number of such data with regard to polydactyly, club-foot, split-foot, etc., occurring among the various aborigines of this country (India).

REFERENCES

GATES, R. R. 1946. *Human Genetics*. 2 Vols. New York: Macmillan. Pp. 1518.

GROHMANN, H. 1939. Zur Erbpathologie der Recklinghausenschen Krankheit. *Erbarzt*, 6: 20–24.

Heredity of the M-N Types

Analysis of Twenty Years' Work

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THE results of studies on the heredity of the M-N types have been collected and analyzed by Wiener (1943) and by Taylor and Prior (1938). While on the whole the findings fit the theory of Landsteiner and Levine (1928) well, Taylor and Prior observed that in their family material there was a statistically significant excess of type MN children in the mating MN × MN (67.5 percent ± 4.2 percent[1] type MN among 56 children). They then scrutinized the work of other authors and found the same discrepancy. Wiener investigated the problem and found that the material from different workers was not homogeneous. In his own family material, among 275 children from MN × MN matings, 51.3 percent ± 2.2 percent belonged to type MN, while in studies by other workers various frequencies had been observed ranging as high as 75.7 percent. Wiener concluded that these discrepancies were due to technical errors, and pointed out that since in this mating children of all types can occur, no special attention would be drawn to errors by inconsistencies with the genetic theory as in other matings. In addition, some of the seeming discrepancies were undoubtedly due to accidental statistical variations.

The problem has recently been revived by Race and Sanger (1950). When analyzing the results of family studies carried out by them, Race and Sanger observed 59.5 percent ± 3.6 percent type MN among 84 children from MN × MN matings, while among 1,029 random bloods tested at the same time with the same sera only 48.98 percent were type MN. The excess of type MN children above the 50 percent expected was nearly significant statistically. Race and Sanger considered therefore that the problem deserves further consideration, because if the excess can be taken at face value this would demonstrate in a direct way the phenomenon of a heterozygote being favored in selection.

After I published the summary of my findings concerning the heredity of the M-N types in 1943, the quantity of family material accumulated more than doubled. The purpose of this paper is to summarize my findings to date, which comprise 1,160 families with 2,734 children, with special regard to the question which has raised concerning the mating MN × MN.

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[1] The figure following the ± sign in this paper represents probable error.

MATERIALS AND METHODS

The families studied were accumulated during a period of twenty years. The earlier material was collected deliberately in order to test Landsteiner and Levine's theory of the inheritance of the M-N types. Later, when studies were conducted on the inheritance of the Rh-Hr types, tests were incidentally carried out for the M-N types. These findings have been published from time to time, the last publications having appeared in 1949. Since that time, additional material has been accumulated, but the present paper will summarize only the published findings.

TABLE 1. HEREDITY STUDIES ON THE M-N TYPES (1929–1949)*

PARENTAL COMBINATIONS	NUMBER OF FAMILIES		CHILDREN BELONGING TO TYPE			TOTALS
			M	N	MN	
M × M	119	Number	272	0	(1)	273
		Per cent	99.6	0	0.4	
M × N	142	Number	(1)	0	315	316
		Per cent	0.3	0	99.7	
N × N	33	Number	0	72	0	72
		Per cent	0	100	0	
MN × M	341	Number	408	(1)	387	796
		Per cent	51.3 ± 1.2	0.1	48.6 ± 1.2	
MN × N	250	Number	(3)	300	334	637
		Per cent	0.5	47.1 ± 1.3	52.4 ± 1.3	
MN × MN	275	Number	163	160	317	640
		Per cent	25.5 ± 1.2	25.0 ± 1.2	49.5 ± 1.3	
Totals.....	1160		847	533	1354	2734

* This table includes: 286 families with 1217 children, reported by Wiener (1943), 47 families with 132 children, reported by Wiener and Landsteiner (1943), 96 families with 273 children, reported by Wiener, Sonn, and Belkin (1944), 109 families with 173 children, reported by Wiener, Sonn, and Polivka (1946), 225 families with 324 children, reported by Wiener, Sonn-Gordon, and Handman (1947), 197 families with 299 children, reported by Wiener (1949), 200 families with 316 children, reported by Wiener, Gordon, and Handman (1949).

All tests were carried out by the same uniform well-slide technique. This technique has already been described in detail elsewhere (Wiener, 1943).

RESULTS

In table 1 are summarized all the investigations on the heredity of the M-N types carried out by the author and his collaborators during the period of 1929–1949. It will be seen that the findings in general conform well with the expectancies under the theory of Lansteiner and Levine. There are, to be sure, six apparent contradictions to the genetic theory (indicated by parentheses in the table), and these will be discussed in greater detail later on. Of particular interest is the mating MN × MN which includes a total of 640 children. There

is almost perfect agreement with the 1M:1N:2MN ratio expected under the genetic theory; thus, there is no excess of type MN children in this large study.

In view of the issue which has been raised concerning the mating MN × MN, it seemed worth while to analyze this mating in greater detail. Therefore, in table 2 we have listed separately the results in this mating from the ten individual studies. It will be seen that the frequency of type MN ranges from 35.0 percent to 58.5 percent, but the overall average is 49.5 percent, and it seems evident that the deviations observed in the individual, smaller studies merely represent accidental statistical variations. No doubt this explanation applies to the deviations observed by Race and Sanger, and by Taylor and Prior.

TABLE 2. ANALYSIS OF MN × MN MATINGS FROM INDIVIDUAL PUBLISHED STUDIES

SOURCE	NUMBER OF FAMILIES	CHILDREN						Totals
		Type M		Type N		Type MN		
		No.	% ± P.E.	No.	% ± P.E.	No.	% ± P.E.	
1. *J. Immun.*, 1931	25	29	25.0 ± 2.7	29	25.0 ± 2.7	58	50.0 ± 3.1	116
2. *Ann. Eugen.*, 1936	18	12	21.0 ± 3.6	17	29.9 ± 4.1	28	49.1 ± 4.5	57
3. *J. Exp. Med.*, 1941	19	22	28.2 ± 3.4	13	16.7 ± 2.8	43	55.1 ± 3.8	78
4. *Genetics*, 1943	7	8	33.3 ± 6.5	4	16.7 ± 5.1	12	50.0 ± 6.9	24
5. *Proc. Soc. Exp. Biol.*, 1943	8	6	30.0 ± 6.9	7	35.0 ± 7.2	7	35.0 ± 7.2	20
6. *J. Exp. M.*, 1944	30	25	29.1 ± 3.3	29	33.7 ± 3.4	32	37.2 ± 3.6	86
7. *Proc. Soc. Exp. Biol.*, 1946	22	9	22.0 ± 4.4	8	19.5 ± 4.2	24	58.5 ± 5.2	41
8. *J. Immun.*, 1947	46	14	22.6 ± 3.6	12	19.3 ± 3.4	36	58.1 ± 4.2	62
9. *Hereditas*, 1949	44	12	17.7 ± 3.1	23	33.8 ± 3.9	33	48.5 ± 4.1	68
10. *Am. J. Human Genet.*, 1949	56	26	29.6 ± 3.3	18	20.4 ± 2.9	44	50.0 ± 3.6	88
Totals	275	163	25.5 ± 1.2	160	25.0 ± 1.2	317	49.5 ± 1.3	640

However, there is hardly any doubt that some of the larger deviations reported in the literature which are statistically significant, were due to technical errors. For example, among 218 children from MN × MN parents one investigator observed 75.7 percent ± 1.9 percent type MN children, and in a second study, the same worker observed among 104 children 59.6 percent ± 3.2 percent type MN children. Another worker found among 98 children from MN × MN matings as many as 66.3 percent ± 3.2 percent type MN children; the same worker in a statistical study on the distribution of the M-N types in the general population found among 430 individuals 57.4 percent ± 1.61 percent type MN individuals. These results indicate that the seeming excess of type MN children in MN × MN matings is due in part to technical errors as well as accidental statistical variations.

With regard to the six seeming exceptions to the genetic theory shown in table 1, five directly involve the supposed father. These five cases constitute exceptions to the law that type M parents cannot have type N children, and that type N parents cannot have type M children. It is significant that no contradiction to this law was found among the 2,734 *mother*-child combinations in these families; nor have we found any contradictions among more than 1500 *mother*-child combinations in cases of disputed paternity (Wiener, 1950). Furthermore, Andresen (1947) has reported that among 20,000 cases of disputed paternity, no contradiction to the genetic theory has been found involving the mother. It seems evident therefore that the five seeming exceptions in our studies involving the *father*, were due to illegitimacy.

The remaining case is a contradiction to the law that the agglutinogens M and N cannot appear in the blood of a child unless present in the blood of one or both parents. Since it has been shown (Wiener, 1943) that for every two exclusions on the basis of the combination $M \rightleftarrows N$, one exclusion is to be expected on the basis of the dominance law, it seems reasonable to conclude that this case also represents an illegitimacy. Thus, the findings summarized in this paper further confirm the accuracy of the theory of Landsteiner and Levine, and justify the application of these tests in medicolegal cases of disputed parentage.

COMMENT

Every serologist has been guilty at some time of accepting his own observations at their literal face value without considering the possibility of errors due to bias when performing the tests, or due to accidental statistical variations. The subconscious tendency to commit such errors is greatest when conducting experiments to verify a particularly attractive hypothesis.

The present analysis demonstrates again the truth of the principle that the most difficult observations to account for are those which do not truly represent the facts. Unfortunately, the blood grouping field, like other fields, is replete with reports presenting such inaccurate observations. In view of the intrinsic complexity of the subject such as the Rh-Hr types, the addition to this of conflicting reports due to inaccurate observations necessarily results in further confusion. Some of the claims, among many others, which there are strong reasons to doubt are reports of sera with extraordinarily high antibody titers reaching the millions, reports of successful desensitization of pregnant Rh-negative women by Rh "hapten" and ethylene disulfonate, claims regarding demonstration of factor Hr_0 (d), and claims that pregnancy with an Rh-negative fetus can cause a rise of Rh antibody titer in the sensitized Rh-negative mother.

SUMMARY

The results of tests for the M-N factors in a series of 1,160 families with 2,734 children are reported. The findings agree well with the genetic theory

of Landsteiner and Levine. There was no excess of type MN children from the mating MN × MN; among 640 children, 49.5 percent belonged to type MN. Previous reports of an excess of type MN children from this mating are due in part to technical errors, and in part to accidental statistical variations.

REFERENCES

ANDRESEN, P. H. 1947. Reliability of the exclusion of paternity after the MN and ABO systems as elucidated by 20,000 mother-child examinations and its significance to the medicolegal conclusion. *Acta path. microb. scand.* 24: 545–553.

LANDSTEINER, K., & LEVINE, P. 1928. On the inheritance of agglutinogens of human blood demonstrable by immune agglutinins. *J. Exp. M.* 48: 731–749.

LANDSTEINER, K., & WIENER, A. S. 1941. Studies on an agglutinogen (Rh) in human blood reacting with anti-rhesus sera and with human isoantibodies. *J. Exp. M.* 74: 309–320.

RACE, R. R., & SANGER, R. 1950. *Blood Groups in Man.* Pp. 290. Oxford: Blackwell.

TAYLOR, G. L., & PRIOR, A. M. 1938. Blood groups in England. III. Discussion of the family material. *Ann. Eugen.*, Cambr. 9: 18–44.

WIENER, A. S. 1943. *Blood Groups and Transfusion.* 3rd Ed. Pp. 438. Springfield, Ill.: C. C. Thomas.

WIENER, A. S. 1949. Heredity of the Rh blood types. VII. Additional family studies with special reference to the genes R^z and r^y. *Hereditas*, 35 (Suppl.): 500–519.

WIENER, A. S. 1950. Heredity of the Rh blood types. IX. Observations in a series of 526 cases of disputed parentage. *Am. J. Human Genet.* 2: 177–197.

WIENER, A. S., GORDON, E. B., & HANDMAN, L. 1949. Heredity of the Rh blood types. VIII. Additional family studies with special reference to factor rh^w. *Am. J. Human Genet.* 1: 127–140.

WIENER, A. S., & LANDSTEINER, K. 1943. Heredity of variants of the Rh type. *Proc. Soc. Exp. Biol.*, N. Y. 53: 167–170.

WIENER, A. S., & SONN, E. B. 1943. Heredity of the Rh factor. *Genetics*, 28: 157–161.

WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1944. Heredity of the Rh blood types. *J. Exp. M.* 79: 235–253.

WIENER, A. S., SONN, E. B., & POLIVKA, H. R. 1946. Heredity of Rh blood types. V. Improved nomenclature; additional family studies with special reference to Hr. *Proc. Soc. Exp. Biol.*, N. Y. 61: 382–390.

WIENER, A. S., SONN-GORDON, E. B., & HANDMAN, L. 1947. Heredity of the Rh blood types. VI. Additional family studies, with special reference to the theory of multiple allelic genes. *J. Immun.*, Balt. 57: 203–214.

WIENER, A. S., & VAISBERG, M. 1931. Heredity of the agglutinogens M and N of Landsteiner and Levine. *J. Immun.*, Balt. 20: 371–388.

ZIEVE, I., WIENER, A. S., & FRIES, J. H. 1936. On the linkage relations of the genes for allergic disease and the genes determining the blood groups, MN types, and eye color in man. *Ann. Eugen.*, Cambr. 7: 163–178.

BIBLIOGRAPHY OF HUMAN GENETICS

THIS section, prepared by the Editor, continues the list of current research articles and books of special interest to students of human heredity, which was started with the first issue of Volume I, covering the year 1949. The present list constitutes part 4 for the year 1950; all publications listed bear the publication date of 1950. Abbreviations used for the titles of medical serials are those which have been adopted by the U. S. Army Medical Library, as published in the *Index-Catalogue of the Library of the Surgeon General's Office*, Fourth Series, volume 10, and in the *Current List of Medical Literature*. Articles published in this *Journal* are not included in the Bibliography.

In order to make the Bibliography of greater service, the address of each author, when known, is added in brackets following the citation. Except as otherwise noted, the address is that of the senior author in cases of multiple authorship. When two or more papers by the same author are listed, the address will be found at the end of the first reference cited. The number [3] in brackets following certain entries in the present list refers to Part 3 of the 1950 list (March, 1951), where the author's address is provided.

1950—PART 4

ANDRÉ VAN LEEUWEN, M., LARUELLE, L., LAUWERS, H., MASSION-VERNIORY, L., & RADERMECKER, J. Epilepsie-myoclonie familiale, sans démence, avec forme partielle (labio-glosso-vélopalatine) et obésité du type glandulaire; étude clinique, électroencéphalographique et généalogique. *Encéphale*, 39(5): 449–471.

ANNING, S. T. Heredity and leg ulcers. *Brit. M. J.* 4692: 1305–1307. [Dermatology Dept., Leeds Gen. Infirmary, Leeds, Eng.]

ANONYMOUS. Genetica ed eugenica. *Rass. stud. psichiat.* 39(5–6): 827–828.

ANONYMOUS. Problema nasledstvennosti pri tuberkuleze. *Probl. Tuberk.*, Moskva, 6: 3–11.

ANONYMOUS. The inheritance of epilepsy. *S. Afr. M. J.* 24(36): 752–755.

ARRICK, M. S. Familial insulin-resistant diabetes mellitus. *J. Clin. Endocr.* 10(7): 840. [Univ. Calif. Hosp., San Francisco, Calif.]

ASHMAN, R. Origins of blood groups ABO, and the European Mongoloid problem. *Am. J. Phys. Anthrop.* 8(4): 426–427. [Dept. Physiol. Louisiana Univ. School of Med., New Orleans, La.]

ASSUS A., & LAFFONT, A. La recherche des groupes sanguines dans le diagnostic de la gémellité unizygotique. *Bull. Ass. gyn. obst. fr.* 2(4): 436–437. [Clin. obstet., 3 Rue Littré, Alger]

ASTALDI, G., TOLENTINO, P., & INVERNIZZI, P. Ricerche sulla genesi della microeritrocitosi. III. Studio eritroblastometrico sui genitori dei malati dei morbo di Cooley. *Minerva pediat.* 2(8): 361–367.

AUER, J. Fingerprints in Eskimos of the northwest territories. *Am. J. Phys. Anthrop.* 8(4): 485–488. [Dept. Anatomy, Univ. Ottawa, Ont., Can.]

AZCOAGA, & BEGUIRISTAIN. Sindrome de Marfan en dos hermanos. *Rev. clin. españ.* 38(6): 438–441. [Hospital Civil, San Sebastián, Spain]

BAILEY, N. T. J. The influence of partial manifestation on the detection of linkage. *Heredity*, 4(3): 327–336. [Dept. Medicine, Univ. Cambridge, Eng.]

BAKX, C. J. A. Erythroblastosis foetalis veroorzakt door het c-antigen. *Ned. tschr. geneesk.* 94(47): 3421–3424.

BATTAGLIA, A. Grupos sanguineos y factor Rh en la poblacion de Buenos Aires. *Prensa med. Argent.* 37(47): 2878–2880. [Hosp. Rivadavia, Buenos Aires, Argent.]

BAUER, J. Is susceptibility to peptic ulcer inherited? *Gastroenterology*, 16(3): 791–793. [Dept. Med., College of Med. Evangelists, Los Angeles, Calif.]

BAUMANN-SCHENKER, R. Über ein neues hereditäres Skelettleiden aus der Gruppe Osteogenesis imperfecta. *Radiol. clin.* 19(5): 332.

BEACHAM, W. D., & BEACHAM, D. W. Sickle-cell disease and pregnancy. *Am. J. Obst.* 60(6): 1217–1228. [Dept. Obstetrics, Tulane Univ. School of Med., New Orleans, La.]

BENTINCK, R. C., LISSER, H., HINMAN, F., & TRAUT, H. C. Familial female pseudohermaphrodism. *J. Clin. Endocr.* 10(7): 818. [Endocrine Clinic., Univ. California Med. School, San Francisco, Calif.]

BERGSTROM, W. H., COOK, C. D., SCANNELL, J. & BERENBERG, W. Situs inversus, bronchiectasis and sinusitis; report of a family with two cases of Kartagener's triad and two additional cases of bronchiectasis among six siblings. *Pediatrics*, 6(4): 573–580. [Syracuse Univ. Med. Center, Syracuse 10, N. Y.]

BIANCO, I. Il midollo osseo nei microcitemici sani e nei malati di anemia microcitica costituzionale. *Policlinico, Sez. med.* 57(5): 241–251. [Istituto di Clinica Medica Generale, Univ. Roma, Italy]

BICKENBACH, W., & KIVEL, F. Mikroskopische Untersuchungen an Erythroblastoseplacenten. *Arch. Gyn.* 177(5): 559–567.

BINDEWALD, H. Beitrag zur Frage einer Beziehung zwischen Rhesus-System und Dysporia entero-bronchopancreatica congenita familiaris (Glanzmann). *Med. Klin.* 45(36): 1137–1140. [Univ.-Kinderklinik, Marburg/Lahn, Germ.]

BÖNI, A., & HAUTMANN, F. Familiäres Vorkommen von Morbus Bechterew in der Schweiz. *Zschr. Rheumaforsch.* 9(9–10): 273–291. [Pestalozzistrasse 10–12, Zürich, Switz.]

BONCINELLI, U., & LOMUTO, G. Documentazione clinica, ricerche e osservazioni su una cheratodermia primitiva familiare del tipo ipercheratosi ittiosiforme congenita. *Rass. derm. sif.* 3(2): 49–63.

BOREK, E., BRECHER, A., JERVIS, G. A., & WAELSCH, H. Oligophrenia phenylpyruvica. II. Constancy of the metabolic error. *Proc. Soc. Exp. Biol.*, N. Y. 75(1): 86–89. [See Jervis]

BORIN, P. Hématologie d'un prématuré aplasie myélo-sanguine chez la mère; myélomatose chez l'enfant. *Sang*, 21(9): 829–833.

BRANDT, S. *Werdig-Hoffmann's infantile progressive muscular atrophy, clinical aspect, pathology, heredity and relation to Oppenheim's amyotonia congenita and other morbid conditions with laxity of joints and muscles in infants.* Copenhagen: Ejnar Munksgaard, 328 Pp. 31 figs.

BREDA, R., & BERNARDI, R. Ostacolo costituzionale alla conversione protrombinica (in membri di famiglia con m. di Rendu-Osler). *Haematologica*, 34(7): 561–586. [Istituto di Clin. Med., Univ. di Milano, Italy]

BRUCE, A. N. Heredity and germ cell continuity. *Edinburgh M. J.* 57(11): 497–514.

BRUYNOGHE, R. Le facteur recessif C. *Ann. Inst. Pasteur*, Par. 79(5): 547–550.

BÜCKLERS, M. Die blauen Augen. *Aerztl. Wschr.* 5(37): 722–723. [Mozartstrasse 18, München-Gladbach, Germ.]

BURGSTEDT, H. Zum Krankheitsbegriff der hereditären Thrombasthenie. *Zschr. Kinderh.* 68(1): 15–24. [Univ.-Kinderklinik, München, Germ.]

CAMPBELL, H. J. The story of genetics. *Biol. Human Affairs*, 16(1): 30–33.

CARAGNA GISPERT, H., DE BRISCO, P. & GARCIA, P. E. Distribución de los grupos sanguineos en 11,704 dadores voluntarios de sangre. *Arch. urug. med.* 37(1): 41–43. [Central de Sangre y Plasma, Facultad de Med., Montevideo, Urug.]

CAZAL, P., & MATHIEU, M. Recherches sur les groupes sanguins du système PQ. *Sang*, 21(8): 717–727. [Centre régional de Transfusion Sanguine, Montpellier, France]

CHENEY, E. A. Heredity, growth and observation as related to extraction procedures. *Am. J. Orthodont.* 36(11): 899–912. [Dept. of Orthodontics, Univ. Michigan, Ann Arbor, Mich.]

CHESSA-PERLE, E. Raro modo di trasmissione della paralisi spinale spastica ereditaria in un ceppo familiare. *Riv. sper. freniat.* 74(2): 273–302. [Clinica d. Malattie Nervose, Univ. di Sassari, Italy]

CLARK, F. B., & PARKER, J. M. Familial polyposis of the colon. *J. Maine M. Ass.* 41(8): 331–336. [Dept. Surg., Maine Gen. Hosp., Bangor, Me.]

CLARK, W. E. L. New discoveries of the Australopithecinae. *Nature*, Lond. 166(4227): 758–760. [Dept. Human Anat., Univ. Museum, Oxford, Eng.]

CLARK, W. E. L. South African fossil hominoids. *Nature*, Lond. 166(4227): 791–792.

COBB, S. W., & BROWN, W. W., JR. Twins with carcinoma of the cervix; a case report. *West. J. Surg.* 58(8): 427–428. [Southwestern Med. College, Dallas 4, Tex.]

COLARUSSO, A. Il morbo di Cooley nell'adulto. *Riforma med.* 64(51): 1379–1388. [Istituto di Clin. Med. Gen., Univ. di Napoli, Italy]

COLARUSSO, A. I gruppi sanguigni nelle emopatie. *Progr. med.*, Nap. 6(22): 725–727.

COMMONS, R. R., BARKER, O. C., & SHELTON, E. K. Sex-linked growth retardation and juvenile diabetes mellitus. *J. Clin. Endocr.* 10(7): 816–817. [Endocrine Clinic, Los Angeles County Gen. Hosp., Los Angeles, Calif.]

CONTE MAROTTA, R., POSTIGLIONE, F., & TROPEANO, L. L'identità patogenetica fra emofilia vera ed emofilia sporadica documentata dall'azione in vitro ed in vivo della sostanza globulinica antiemofilica. *Progr. med.*, Nap. 6(21): 685–691.

COOK, B. A. Mongolism in one of twins; report of 2 cases. *Med. J. Australia*, 2(12): 445–446. [Bulli, New South Wales]

CORBEIL, & BESSERRE. Trois cas de dysplasies de Capdepont dans la même famille. *Odontologie*, 71(11): 583–586. [Dept. Stomatol., Hôpitaux Bégin, Paris, France]

CORNACCHIONE, M., GOTLIB, M. H., HUSE, W., & TAUBE, J. I. Twins: one macerated, the other near term and normal. *J. Indiana M. Ass.* 43(12): 1207–1210. [814 S. East St., Indianapolis 2, Ind.]

CROZIER, T. H., & CAMPBELL, W. A. B. Mongolism in one of twins. *Brit. M. J.* 1(4684): 869–870. [Royal Victoria Hosp., Belfast, N. Ireland]

CSORBA, A. Laurence-Moon-Biedl syndrome; three cases in one family. *Confinia neur.* 10(6): 378–386. [Neuropsych. Clinic, Pázmány Péter Univ. Budapest, Hung.]

CUTBUSH, M., & MOLLISON, P. L. The Duffy blood group system. *Heredity*, 4(3): 383–389. [M. R. C. Blood Transfusion Research Unit, Ducane Rd., London W. 12, Eng.]

DAHR, P. Über Rh-bedingte Transfusionszwischenfälle; Bericht über 24 eigene Fälle. *Arch. klin. Chir.* (Langenbeck's) 266(1): 83–105. [Inst. f. Blutgruppenforschung, Göttingen, Germ.]

DALE, H. The science of genetics. *Carib. M. J.* 12(3–4): 96–98.

DE BELLIS, L. Sulla comparsa degli antigeni A, B, O e D negli eritrociti umani durante la vita prenatale. *Q. clin. ostet.* 5(12): 777–782.

DE KROMME, L. Betekenis van de antilichaamvariëteiten. *Ned. tschr. geneesk.* 94(47): 3426–3427.

DELAY, J., & PICHOT, P. Les troubles métaboliques et l'hypopigmentation dans les oligophrénies phénylpyruviques. *Sem. hôp.*, Par. 26(41): 1962–1967. [Clinique des Maladies Mentales, Paris, France]

DELBOS, J. Virilisme pilaire familial à caractère dominant; virilisme pilaire chez la mère; polydysplasie hyperplasique (syndrome de Schaefer) chez la fille. *Lyon méd.* 183(36): 157–159. [Toulon, France]

DESGREZ, H., LEDOUX-LEBARD, G., KIRSCH, & ATRI. La maladie ostéogénique; exostoses et chrondromes: hérédité, dégénérescence. *J. radiol. electr.* 31(7–8): 488–493.

DÍAZ DE YRAOLA, G. El factor Rh: generalidades respresentación esquematica de sus variedades y genotipos. *Rev. clín. españ.* 39(4): 233–239. [Inst. Provincial de Sanidad, Sevilla, Spain]

DRAGOTTI, G. La morale eugenica. *Policlinico, Sez. prat.* 57(48): 1576–1578.

DUVERNE, J., BONNAYMÉ, R., MOUNIER, R., & FLAISSIER. Néphrite scabiéique familiale. *Lyon méd.* 183(30): 62–63. [St. Etienne, France]

EXPOSITO, L., & PONCE DE LEON, A. Braquidactilia familiar seguida en cinco generaciones. *Rev. cubana pediat.* 22(9): 550–559.

FABERGÉ, A. C. Genetic effects in man from atomic explosions and from chronic irradiation. *Science*, 112(2917): 628.

FARQUHAR, H. G. Congenital toxoplasmosis; report of two cases in twins. *Lancet*, Lond. 2(21): 562–564. [Royal Liverpool Children's Hosp., Liverpool, Eng.]

FARRIS, J. M., & BISHOP, R. C. Surgical aspects of abnormal twinning. *Surgery*, 28(2): 443–453. [Dept. Surgery, Moore-White Clinic, Los Angeles, Calif.]

FENICHEL, R. L., WATSON, J., & EIRICH, F. Electrophoretic studies of the plasma and serum proteins in sickle cell anemia. *J. Clin. Invest.* 29(12): 1620–1624. [State Univ. of N. Y. College of Med., Brooklyn, N. Y.]

FERNANDES, J. F. Oligofrenia fenilpirúvica em melanoderma. *Brasil méd.* 64(42–43): 225. [Cadeira de Química Fisíol., Fac. de Med., Univ. de Minas Gerais, Brazil]

FILITTI-WURMSER, S., JACQUOT-ARMAND, Y., & WURMSER, R. Sur la combinaison des isohémagglutinines avec les groupes agglutinogènes. *J. Chim. phys.* 47(5–6): 419–431.

FOIS, A. Anemia emolitica acquisita con impronta familiare in un lattante. *Pediatria*, Nap. 58(9–10): 749–754.

FORNARI, A. Sull'allestimento di siero anti-O per uso di laboratorio. *Boll. Soc. ital. biol. sper.* Nap. 26(6): 1008–1010. [Istituto di Med. Legale, Univ. di Pisa, Italy]

FORTEZA BOVER, G., SORRIBES-SANTA MARIA, V. & MARCO ORTS, F. Anemia mediterranea infantil (enfermidad de Cooley). *Rev. españ. pediat.* 6(5): 673–684.

FRASER, T. N. Ankylosing spondylitis in sisters. *Ann. Rheumat. Dis.* 9(3): 231–236. [Gardiner Institute of Med., Univ. Glasgow, Scotl.]

GABRIEL, A. C. Genetics and the teeth. *Dent. J. Australia*, 22(5): 237–241. [Dept. Anatomy, Univ. Sydney, Australia]

GALGANO, M. Aspetti genetici di alcuni problemi del sesso. *Riv. biol.* 42(2): 215–237. [Univ. degli Studi, Palermo, Italy]

GARBER, M. J. Misshapen toes in three generations of the G. family. *J. Hered.* 41(8): 215–216.

GATES, R. R. Ethnobotany and blood groups of British Columbia Indians. *Canad. M. Ass. J.* 62: 383–384. [Peabody Museum, Harvard Univ., Cambridge 38, Mass.]

GATTO, I. Ricerche ematologiche su due casi de anemia drepanocitica. *Boll. Soc. ital. biol. sper.*, Nap. 26(6): 911–912. [Clinica Pediatrica, Univ. Palermo, Sicily]

GIESEKING, H. Das familiäre Auftreten von "jugendlichen Knochencysten." *Chirurg*, 21(12): 670–672.

GILBEY, B. E. An Rh allele on the E-e locus reacting with both anti-E and anti-e sera. *Brit. J. Exp. Path.* 31(6): 695–702. [Path. Dept., West Middlesex Hosp., Isleworth, Eng.]

GINI, C. Sur la détermination du sexe chez l'homme. *Sem. hôp.*, Par. 26(88): 4560–4562. [Via Terme 10, Roma, Italy]

GIRAUD, G. La valeur séméiologique de l'hyperuricémie. *Montpellier méd.* 37–38(5): 347–360.

GOODHILL, V. The nerve-deaf child: significance of Rh, maternal rubella and other etiologic factors. *Ann. Otol. Rhinol.* 59(4): 1123–1147. [3]

GOUGEROT, H. La priorité du pemphigus chronique familial héréditaire bénin. *Ann. derm. syph.* 10(4): 361–363.

GROSJEAN, R. Nouvelles recherches sur l'agglutinogène P. *C. rend. Soc. biol.*, Par. 144(13–14): 1010–1011. [Lab. de Méd. légale, Univ. de Liége, Belg.]

GROSJEAN, R. Sur l'hérédité de l'agglutinogène P. *C. rend. Soc. biol.*, Par. 144(13–14): 1011–1013.

GROSSMAN, M. I., & IVY, A. C. Heredity and peptic ulcer. *Gastroenterology*, 16(3): 793–794. [Univ. Illinois College of Med., Chicago 12, Ill.]

GRUNDLER, E. Besonderheiten im Ablauf der haemolytischen Krisen beim familiären Ikterus des Säuglings. *Zschr. Kinderh.* 68(4): 297–302. [Univ.–Kinderklinik, Tübingen, Germ.]

GUARIENTO, A. Prenhez hétero-especifica. *Rev. gin. obst.*, Rio, 44(2): 553–574.

HADIDA, E. & BERANGER, J. Alopecie congénitale chez deux frères. *Bull. Soc. fr. derm. syph.*, Par. 57(4): 424–425.

HAILE, H. Erfahrungen der Tübinger Frauenklinik an 35 Rh-bedingten Erythroblastosefällen. *Zschr. Geburtsh. Gyn.* 133(2): 207–243. [3]

HALLGREN, B. *Specific Dyslexia ("Congenital Word-Blindness"), A Clinical and Genetic Study.* Copenhagen: Munksgaard. Pp. 287, with 3 figs. Also published in *Acta psychiat. neur.*, Kbh. Suppl. 65. [Karolinska Inst., Stockholm 60, Swed.]

HARRIS, C. Blood groups and anthropology. *Manitoba M. Rev.* 30(9): 624–625.

HARRIS, J. W. Studies on the destruction of red blood cells. VIII. Molecular orientation in sickle cell hemoglobin solutions. *Proc. Soc. Exp. Biol.*, N. Y. 75(1): 197–201. [Dept. Medicine, Harvard Med. School, Boston, Mass.]

HAZEL, L. N., & LUSH, J. L. Computing inbreeding and relationship coefficients from punched cards. *J. Hered.* 41(11): 301–306. [Dept. Animal Husbandry, Iowa State College, Ames, Iowa]

HERON, I. C. Familial diaphragmatic hernia. *California M.* 73(6): 497–499. [490 Post St., San Francisco 2, Calif.]

HOFSTEN, N. VON. Ärftliga ryggradsvariationer som bevismedel vid faderskapsprövning. *Nord. med.* 43(22): 908–911. [Zoologiska Institutionen, Univ. Uppsala, Swed.]

HOŘEJŠÍ, J., PÍSAŘOVICOVÁ-ČIŽKOVÁ, J., & VANĚK, J. Glycogenosis: Familární smišená forma u dvou sester. *Pediat. listy*, 5(5): 259–265.

HOWE, C., & RUSTIGIAN, R. Studies with the Rh_0 (D) antigen. *J. Immun.*, Balt. 64(6): 505–513. [Dept. Bacteriology, Harvard Med. School, Boston, Mass.]

HUFNAGEL, L. Verrucose séborrhéique diffuse, polypomatose mamelonnaire et kératose pilaire, maladie familiale héréditaire et précancéreuse s'apparrentant avec l'épidermodysplasie verruciforme. *Bull. Soc. fr. derm. syph.*, Par. 57(4): 398–400.

INGELRANS, P., VANLERENBERGHE, H., & LACHERETZ, M. Maladie de Little chez deux jumeaux monozygotes. *Rev. orthop.* 36(5): 320–321.

ISAACS, R. Sickling: a property of all red blood cells. *Science*, 112(2920): 716–718.

ISRAEL, M. Hereditary aspects of arteriosclerosis. *Med. Rec.*, N. Y. 163(9): 219–232. [Vascular Research Foundation, Roslyn, N. Y.]

JAEGER, W. Systematische Untersuchungen über "inkomplette" angeborene totale Farbenblindheit: eine "Zwischenform" zwischen angeborener totaler Farbenblindheit und Protanopie. *Arch. Ophth.* Berl. 150(5–6): 509–528. [Univ.-Augenklinik, Heidelberg, Germ.]

JERVIS, G. A. Excretion of phenylalanine and derivatives in phenylpyruvic oligophrenia.

Proc. Soc. Exp. Biol., N. Y. 75(1): 83–86. [Research Dept., N. Y. State Dept. Ment. Hygiene, Thiells, N. Y.]

JONES, W. A., GERRIE, J., & PRITCHARD, J. Cherubism—a familial fibrous dysplasia of the jaws. *J. Bone Surg.*, Brit. Ed., 32–B(3): 334–347.

JONKERS, G. H. Familial ptosis congenita combined with other congenital defects of motility of the ocular musculature. *Ophthalmologica*, 120(5): 372–374. [Gorinchem, Netherl.]

KALMUS, H., & GATES, R. R. Taste reactions to antithyroid substances. *Science*, 112(2912): 475. [Dept. Zoology, Indiana Univ., Bloomington, Ind.]

KAMMERER, T. Trois cas d'épilepsie concordante chez des jumeaux. *Encéphale*, 39(6): 568–579. [14 Ave. de Vosges, Strasbourg, France]

KAPLAN, I. I. Do children born of offspring of mothers irradiated for sterility show abnormal genetic effects? *Arch. Pediat.* 67(12): 569–572. [755 Park Ave., New York 21, N. Y.]

KEIFER, W. S., WORTHAM, J. T., ZANARTU, J., & HAMBLEN, E. C. The Laurence-Moon-Biedl syndrome; a confused symptom-complex. *Am. J. Obst.* 60(4): 721–730. [Division of Endocrinol., Duke Univ. School of Med., Durham, N. C.]

KEIZER, D. P. R. Hypertelorisme gepaard gaande met polydactylie, hyperphalangie en digiti spatulaformes. *Mschr. kindergeneesk.* 18(10): 373–375. [3]

KINNEY, C. E. The pathology of hereditary deafness. *Ann. Otol. Rhinol.* 59(4): 1117–1122. [10515 Carnegie Ave., Cleveland 6, Ohio]

KLEIN, M. Hereditary bilateral ptosis and blepharophimosis associated with other developmental abnormalities of the outer eye. *Proc. R. Soc. M.*, Lond. 43(12): 1025–1026.

KLEINSCHMIDT, W. H., & SCHWARTZ, S. O. Familial hereditary hemorrhagic telangiectasia in the Negro; report of a second case. *Illinois M. J.* 98(5): 298–300. [Cook County Hosp., Chicago 12, Ill.]

KNOLL, W. Beitrag zur Cooley-Anämie. *Schweiz. med. Wschr.* 80(41): 1113. [Alpnachstad, Switz.]

KOECHLIN, H. Fistules congénitales de la lèvre inférieure, transmises à travers quatre générations. *Praxis*, 39(43): 918–920.

KRATKOVÁ, E., & ROKOS, J. Klippel-Feilův syndrom při inkompatabilitě Rh systému. *Pediat. listy*, 5(6): 352–355.

LAFFONT, A., & ASSUS, A. Consanguinité et antagonisme Rh. *Sang*, 21(6): 523–527.

LANGE, R. D., MINNICH, V., & MOORE, C. V. In vitro differences in behavior of sickle cell anemia and trait erythrocytes produced by variations in O_2 tension and pH. *J. Laborat. Clin. M.* 36(5): 848. [3414 Lindell Blvd., St. Louis 3, Mo.]

LANINI, G. A propos d'une famille d'hémophiles du Valais central. *Rev. méd. Suisse rom.* 70(10): 678–681. [Sanatorium populaire valaisan, Montana, Switz.]

LAWRENCE, J. H., & GOETSCH, A. T. Familial occurrence of polycythemia and leukemia. *California M.* 73(4): 361–364. [Donner Lab. of Med. Physics, Univ. California, Berkeley 4, Calif.]

LECOMTE, M. Eléments d'hérédopathologie. *Scalpel*, Brux. 103(42): 1051–1060; 103(43): 1071–1082; 103(44): 1104–1114; 103(45): 1133–1145.

LEHMANN, W. Aspermie bei Söhnen aus einer Verwandtenehe. *Med. Klin.* 45(36): 1157. [Elsdorf, Kr. Rendsburg, Germ.]

LESIEUR. A propos d'un cas familial de cirrhose bronzée. *Arch. mal. app. digest.* 39(9–10): 960–962. [Saint-Brieuc, France]

LEUBA, J. Le milieu et la névrose familiale. *Sem. hôp.*, Par. 26(47): 2273–2277.

LEVER, W. F., & MACLEAN, J. G. Primary familial xanthomatosis and biliary xanthomatosis

(biliary cirrhosis with xanthomatosis). *J. Invest. Derm.* 15(3): 173–180. [270 Commonwealth Ave., Boston 16, Mass.]

LINCOLN, M. What can happen when diabetics marry? *Northwest, M.* 49(7): 466–467. [1215 4th Ave., Seattle 1, Wash.]

LÖNS, M. Der positive Vaterschaftsnachweis. *Zschr. Hyg.* 131(4): 371–385; 131(6): 609–613. [Hygienisches Inst. der Stadt Dortmund, Germ.]

LOMBARD, H. L., & POTTER, E. A. Epidemiological aspects of cancer of the cervix, II. Hereditary and environmental factors. *Cancer*, N. Y. 3(6): 960–968. [100 Nashua St., Boston 14, Mass.]

LOPASHOV, G. V., & STROEVA, O. G. Razvitie immunologicheskikh reaktsii i problema hecovmestimosti tkanei pri peresadkakh. *Usp. Sovrem. biol.* 30(2/5): 234–257.

LORENZ, T. H., KURTZ, C. M., & SHAPIRO, H. H. Cardiopathy in Friedreich's ataxia (spinal form of hereditary sclerosis); review of literature and analysis of cases of five siblings. *Arch. Int. M.* 86(3): 412–426. [Univ. Wisconsin School of Med., Madison 6, Wisc.]

LUCIANI, A., & MASSEI, G. Comportamento del tasso di isoagglutinine del siero nel corso delle malattie infettive. *Minerva med.*, Tor. 41(51); 709–712. [Clinica Med. Gen., Univ. di Pisa, Italy]

LUDWIG, A., & KORTING, G. Vogt-Koyanagi-ähnliches Syndrom und mandibulofaciale Dysostosis (Franceschetti-Zwahlen). *Arch. Derm. Syph.*, Berl. 190(4): 307–316. [Univ.-Augenklinik, Skopje, N. R. Makedonia, Jugoslavia]

LUSTIG, B. Zur Identität von Zwillingsdepressionen. *Nervenarzt.* 21(10): 440–442. [Psychiat. Abteilung, Städtisches Krankenanstalten, Lübeck, Germ.]

MCCOLL, M. G. The influence of heredity on mental diseases. *Med. Press*, London 224(22): 529–533. [Rainhill Mental Hosp., Rainhill, Liverpool, Eng.]

MARCOLONGO, F., CARCASSI, U., & ARGIOLAS, N. Modificazioni indotte dal disordine ematologico mediterraneo sul quadro morfologico di alcune eritropatie primitive o secondarie sovrapposte ad esso. *Haematologica*, 34(6): 491–504. [Instituto di Patologia, Univ. di Cagliari, Italy]

MARIE, J., SERINGE, P., BOISSIÈRE, H., & HÉBERT, S. Ichtyose foetale familiale. *Nourrisson*, 38(6): 257–266.

MARIOTTI, L. Contributo alla sindrome di Marfan (aracnodattilia ed ectopia della lente), con particolare riguardo alla sintomatologia oculare ed alla ereditarietà; 2 casi. *Ann. ottalm.* 76(11): 361–372.

MATTHEWS, W. B. Familial ataxia, deafmutism and muscular wasting. *J. Neur.*, London 13(4): 307–311. [Univ. Dept. Neurology, Royal Infirmary, Manchester, Eng.]

MELANOWSKI, W. H. Podstawowe zagadnienia dziedziczności w okulistyce. *Polski tygod. lek.* 5(26): 1021–1025.

MELE, L. Ulteriore contributo allo studio del morbo di Cooley. *Pediatria*, Nap. 58(9–10): 755–764.

MILLET, M., & HUBINONT, P. O. Sur un caractère différentiel des agglutinines naturelles et des agglutinines d'immunisation. *Ann. Inst. Pasteur*, Par. 79(5): 737–748.

MILLS, H., HUFF, R. L., KRUPP, M. A., & GARCIA, J. F. Hemolytic anemia secondary to a familial (hereditary) defect in hemoglobin synthesis; report of a case with radioiron studies. *Arch. Int. M.* 86(5): 711–726. [Dept. Med., San Fransico Vet. Admin. Hosp., Long Beach, Calif.]

MONIE, I. W. Three pedigrees of congenital auricular sinus. *J. Hered.* 41(8): 219–222. [Univ. Manitoba, Winnipeg, Man., Canada]

MORRIS, R. W., & JACOBS, L. M. On the application of somatotyping to the study of con-

stitution in disease. *S. Afr. J. Clin. Sc.* 1(4): 347–370. [Dept. Medicine, Univ. Witwatersrand, Union So. Africa]

MOSKOWITZ, M., DANDLIKER, W. B., CALVIN, M., & EVANS, R. S. Studies on the antigens of human red cells. I. Separation from human erythrocytes of a water soluble fraction containing the Rh, A and B factors. *J. Immun.* 65(4): 383–392.

MÜLLER, H. Zur Frage der Beziehung zwischen Flimmer- und Lokaladaptation: Untersuchung an Personen mit angeborener Störung des Farbensinnes. *Arch. Ophth.*, Berl. 151(1–2): 136–155. [Univ. Augenklinik, Heidelberg, Germ.]

NACHTSHEIM, H. Die Frage der Sterilisation vom Standpunkt des Erbbiologen. *Berl. Gesundheitsblatt*, 1(24).

NICKERSON, J. L., GREGERSEN, M. I., ROOT, W. S., & SHARPE, L. M. Influence of blood incompatibilities on measurement of blood volume by cell-tagging methods. *Proc. Soc. Exp. Biol.*, N. Y. 75(1): 61–62. [Dept. Physiol., College of Phys. & Surg. Columbia Univ., N. Y. C.]

NORDMEYER, N. Serologische Beobachtungen bei familiärer Erythroblastose. *Med. Klin.* 45(39): 1250–1252. [Kirchröderstrasse 2, Hanover, Germ.]

OLSON, W. C., & HUGHES, B. O. Growth patterns of exceptional children. Chapt. IV, Forty-ninth *Yearb. Nat. Soc. Study of Education*, Pt. II. pp. 61–82. [Dept. Education, Univ. Michigan, Ann Arbor, Mich.]

PAJTÁŠ, J. Case de pseudogliome familial héréditaire dans trois générations (Retinitis exsudativa Coats). *Ophthalmologica*, 120(6): 411–415. [3]

PAJTÁŠ, J. Prípad Doyne's family honeycomb "choroiditis." *Cesk. oft.* 6(5):

PEABODY, J. W., PEABODY, J. W., JR., HAYES, E. W., & HAYES, E. W., JR. Idiopathic pulmonary fibrosis; its occurrence in identical twin sisters. *Dis. Chest.* 18(4): 330–344. [1746 K St. N. W., Washington 6, D. C.]

PELIKÁN, L. Dysostosis enchondralis epiphysaria u 2 sourozencú. *Pediat. listy*, 5(5): 273–276.

PETERSON, B. H. Congenital deafmutism, pigmentary degeneration of the retina and amentia. *Med. J. Australia*, 2(24): 854–858. [Dept. of Publ. Health, Canberra, New South Wales]

PFÄNDLER, U. Une forme récessive simple de la dystrophie musculaire progressive. *Arch. Julius Klaus Stift.* 25(3–4): 544–549. [La Chaux-de-Fonds, Switz.]

PFÄNDLER, U., & COTTET, P. Une souche de Sugnens (Vaud) atteinte d'une dysplasie osseuse et unguéale héréditaire; démonstration d'un linkage autosomal de facteurs. *Arch. Julius Klaus Stift.* 25(3–4): 598–602.

PHANSOMBOON, S., & POLLACK, O. J. Study of an American Negro family with the rare Rh genotype $r^y r$ (CdE/cde). *J. Immun.* 65(6): 711–714. [Siriraj Hosp., Bangkok, Thail.]

QUATTRIN, N. Sulle emopatie familiari; studio su 64 casi di ittero constituzionale cosiddetto emolitico atipico. *Minerva med.*, Tor. 41(54): 815–821. [3]

QUATTRIN, N. Sulle emopatie familiari; aspetti attuali e meno noti di ereditarietà nelle emopatie umane. *Minerva med.*, Tor. 41(56): 919–924.

QUATTRIN, N. Clinica delle trombopatie. *Progr. med.* Nap. 6(11):

RAMOS BÁEZ, P. Algunas nociones sobre la intervención de los fenómenos de desequilibrio iónico en los fenómenos de desequilibrio biológico y posiblemente en los fenómenos de las mutaciones biológicas. *Rev. med. cubana*, 61(3): 149–174. [Balneario de San Miguel de los Baños, Matanzas, Cuba]

RANGIER, M., & DE TRAVERSE, P. M. Les pentosuries. *Presse med.* 58(81): 1416–1417. [Inst. Biol., Hôpital Cochin, Paris, France]

RAUCH, H. W. M. Gicht bei einem 3½ jährigen Mädchen. *Med. Mschr.* 4(12): 931–933.

RECORD, R. G., & MCKEOWN, T. Congenital malformations of the central nervous system; maternal reproductive history and familial incidence. *Brit. J. Social M.* 4(1): 26–50. [3]

REICHMAN, H. R. Familial adenomatosis. *J. Internat. Coll. Surgeons*, 14(6): 700–708. [Dept. Surgery, Univ. Utah, Salt Lake City 1, Utah]

REINBERG, M. H. Progressive muscular dystrophy associated with retinitis pigmentosa. *California M.* 73(3): 266–268. [Los Angeles County Gen. Hosp., Los Angeles, Calif.]

REYNOLDS, G. The heart in arachnodactyly. *Guy's Hosp. Rep.*, Lond. 99(2–3): 178–208. [Cardiac Dept., Guy's Hosp., London S.E. 1, Eng.]

RUTLEDGE, L. H. An unusual type of pulmonary disease involving six members of a family. *Minnesota M.* 33(7): 694–699. [Detroit Lakes, Minn.]

SACHS, H. W., & TRENTMANN, H. Auftreten fötaler Erythroblastose bei A_1-Kindern und Ausbleiben bei A_2-Kindern in einer Familie mit A_1-O-Inkompatibilität. *Deut. med. Wschr.* 75(39): 1301–1302. [Wichertstrasse 10, Berlin N 113, Germ.]

SAEZ, F. A. Genetica y evolución. *Cienc. & invest.* 6(12): 531–539.

SALLERAS, A., & ORTIZ DE ZÁRATÉ, J. C. Recessive sex-linked inheritance of external ophthalmoplegia and myopia coincident with other dysplasias. *Brit. J. Ophth.* 34(11): 662–667. [Dept. Ophthalmology, Univ. of Buenos Aires, Argent.]

SCHACHTER, M. Régression affective et psychomotrice chez des jumelles univitellines; rôle des facteurs mésologiques. *Arch. internat. neur.* 69(9): 170–173. [1 Rue Molière, Marseille, France]

SCHILLING, R. Über die Stimme erbgleicher Zwillinge. *Folia phoniat.* 2(4): 205–238. [Freiburg i. Br., Germ.]

SCHMID, J. Ein Beitrag zur Ursache der Hämophilie. *Wien. klin. Wschr.* 62(40): 752–756. [II Medizinische Univ.-Klinik, Wien, Austria]

SCHNEIDER, R. G., & LEVIN, W. C. Production of specific antisera against sickle cell anemia erythrocytes; antibody in sicklemia sera. *Proc. Soc. Exp. Biol.*, N. Y. 75(1): 110–114. [Dept. Neurology and Psychiat., Univ. Texas Med. Branch, Galveston, Tex.]

SCHNEIDER, R. G., & LEVIN, W. C. Production of specific anti-sera against erythrocytes from patients with sicklemia. *J. Laborat. Clin. M.* 36(6): 985.

SCHNEIDER, R. W., & CORCORAN, A. C. Familial nephrogenic osteopathy due to excessive tubular reabsorption of inorganic phosphate; a new syndrome and a novel mode of relief. *J. Laborat. Clin. M.* 36(6): 985–986. [2050 E. 93rd St., Cleveland 6, Ohio]

SCHRADER, A. Bemerkungen zur familiären multiplen Sklerose. *Deut. Zschr. Nervenh.* 164(5–6): 469–479. [Moorenstrasse 5, Düsseldorf, Germ.]

SCHROEDER, W. A., KAY, L. M., WELLS, I. C., GERKE, C., & MOSS, J. Amino acid composition of hemoglobins of normal Negros and sickle-cell anemics. *J. Biol. Chem.* 187(1): 221–240. [Gates & Crellin Labs. Calif. Inst. Technology, Pasadena, Calif.]

SEMERARI, A. Recenti vedute sull'ereditarietà della schizofrenia. *Rass. neuropsich.* 4(5): 513–526.

SILLEVIS SMITT, W. G. Neurofibromatose van het gelaat met skelatafwijkingen. *Ned. tschr. gencesk.* 94(40): 2888–2894. [Neur. Kliniek, Rijksuniversiteit, Utrecht, Netherl.]

SILVER, H. K. Mediterranean anemia in children of non-Mediterranean ancestry. *Am. J. Dis. Child.* 80(5): 767–778. [Univ. California Hosp., San Francisco 22, Calif.]

SIMMONS, R. T., GRAYDON, J. J., & SEMPLE, N. M. The A_1-A_2-B-O, M-N and Rh blood groups in Southern Chinese: Hak-Kas, Cantonese and Hokkiens. *Med. J. Australia*, 2(26): 917–922. [Commonwealth Serum Labs., Melbourne, Australia]

SINGER, K., MOND, E., HYMAN, J., & LEVY, R. C. Circulating anticoagulants in hemophilia and in hemophilia-like disease. *Blood*, 5(12): 1135–1149. [Dept. Biochem., Michael Reese Hosp., Chicago 16, Ill.]

SLOBOZIANO, H., & GULEŞIU, T. Contribution à l'étude des anomalies oculaires dans la dolicosténomélie. *Arch. opht.*, Par. 10(4): 500–504.

SONDERMANN, R. Die Bedeutung der Vererbung für die Entwicklung der Myopie. *Arch. Ophth.*, Berl. 151(1–2): 200–208. [Gummersbach (Rhld), Germ.]

SPEISER, P., & LEWKIN, D. Über den Blutfaktor Kell und seine Häufigkeit in der Wiener Bevölkerung. *Klin. Med.*, Wien, 5(12): 529–534. [3]

SPEISER, P., & SCHWARZ, J. Zur Kenntnis der Persistenz von Antikörpern gegen den Rhesusfaktor im Serum Immunisierter. *Wien. klin. Wschr.* 62(40): 770–775.

STANBURY, J. B., & HEDGE, A. N. A study of a family of goitrous cretins. *J. Clin. Endocr.* 10(11): 1471–1484. [Massachusetts Gen. Hosp., Boston 14, Mass.]

STEINBERG, A. G., & WILDER, R. M. A reconsideration of the phenomenon of anticipation in diabetes mellitus. *Proc. Mayo Clin.* 25(23): 625–630 [Mayo Clinic, Rochester, Minn.]

STEPHENS, F. E., & NUNEMAKER, J. C. Spondylitis in identical twins reared apart. *J. Hered.* 41(11): 283–286, frontispiece. [Lab. Human Genet., Univ. Utah, Salt Lake City 1, Utah]

STEVENS, W. L. Statistical analysis of the A-B-O blood groups. *Human Biol.*, 22(3): 191–217. [Faculdade de Ciênc. Econ., Univ. de São Paulo, Rua Vila Nova, São Paulo, Braz.]

STOCKING, B. W. Carcinoma of the cervix uteri in identical twins. *Cancer*, N. Y. 3(6): 969–971. [2400 University Ave., Muncie, Ind.]

STOLINSKY, A. Some facts about genetics of special interest to physicians. *Med. Rec. N. Y.* 163(11): 263–270. [142-18th Ave., San Francisco, Calif.]

STRANSKY, E. Über kongenitalen, familiären, nicht-hämolytischen Icterus. *Ann. paediat.* 175(4): 301–307.

STRAZZI, A. L'importanza dell'ambliopia nello strabismo ereditario. *Boll. ocul.*, Bologna, 29(8): 527–536.

STÜTTGEN, G. Die Vitiligo in erbbiologischer Betrachtung. *Zschr. Haut & Geschlkr.* 9(11): 451–457.

SYLVEST, B. Laebefistler hos tvillinger. *Nord. med.* 44(37): 1487.

SZYMKIEWICZ, T. Bardzo rzadki zespót Pelger-Hueta. *Polski tygod. lek.* 5(26): 1013–1017.

TAGLIAFERRO, E., & NAVAZIO, F. Sull'anomalia di Pelger-Huiet. *Minerva med.*, Tor. 41(52): 729–732. [Ospedale Maggiore di Trieste, Trieste, Italy]

TANCREDI, G. Il comportamento del ricambio emoglobinico e delle resistenze globulari osmotiche nel morbo di Cooley. *Riforma med.* 64(50): 1357–1359. [Istituto di Semeiotica Med., Univ. di Napoli, Italy]

TEGELAERS, W. H. H. Familiaire congenitale neuroectodermale dysplasie. *Mschr. kindergeneesk.* 18(10): 376–380.

TEINDEL, H. Familiäre Vitiligo. *Zschr. Haut & Geschlkr.* 9(11): 457–462.

TERRY, M. C. Taste-blindness and diabetes in the colored population of Jamaica. *J. Hered.* 41(11): 306–307. [Kingston Public Hosp., Kingston, Jamaica]

THERMAN, E., & TIMONEN, S. Multipolar spindles in human cancer cells. *Hereditas*, 36: 393–405. [Woman's Hosp., Univ. Helsinki, Finl.]

THOMPSON, M. W., LAAKSO, L. E., & WATSON, E. M. Studies of the inheritance of diabetes mellitus. I. The relation of heredity and the age of onset of diabetes. *Canad. M. Ass. J.* 63(6): 556–559. [Dept. Anat., Univ. Alberta, Edmonton, Alb., Can.]

TIMONEN, S. Mitosis in normal endometrium and genital cancer. *Acta obst. gyn. scand.* 31 (Suppl. 2): 1–88, illust. [3]

TIMONEN, S., & THERMAN, E. Variation in the somatic chromosome number in man. *Nature*, Long. 166(4232): 995–996.

TOWEND, B. R. Twins. *Dent. Rec.* 70(9–10): 217–218.

TRIER, M. On Reiter's syndrome, with special reference to cardiac complications and familial occurrence of the syndrome. *Acta med. scand.* Suppl. 239: 123–128. [Med. Dept. B, Rigshospital, Copenhagen, Denm.]

TRILLOT J. De l'avortement eugénique et d'un eugénisme lícite. *Ann. méd. lég.* 30(4): 204–210. [Albi, France]

TURPIN, R., & SCHÜTZENBERGER, M. P. Sur la détermination du sexe chez l'homme. *Sem. hôp.*, Par. 26(88): 4562–4563. [Hôpital St. Louis, Paris X, France]

UNDRITZ, E. Anomalies héréditaires des cellules du sang. *Rev. hémat.* 5(5–6): 644–695. [Lab. de Pharmacologie de Sandoz S.A., Bâle, Switz.]

VACHON, A., LEHMANN, E., & CHEVALLIER, G. A propos des ulcères gastro-duodénaux familiaux: ulcère chez deux jumeaux univitellins. *Arch. mal. app. digest.* 39(9–10): 1012–1013.

VAN BOGAERT, L. Sur une athétose double (état marbré) chez un frère et une soeur; la famille Van Hoe; evolution de nos conceptions sur l'athétose double. *Mschr. Psychiat.* 120(3–4): 169–205. [Institut Bunge, Berchem-Anvers, Belg.]

VANDENBERG, H. J. Can cancer be an inherited family disease? *J. Michigan M. Soc.* 49(10): 1185–1187. [1810 Wealthy St., S. E., Grand Rapids 6, Mich.]

VAN DER HEIDE, H. M. De betekenis van het bloedgroepenonderzoek voor de anthropologie. *Ned. tschr. geneesk.* 94(47): 3418–3421. [Central Lab., Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherl.]

VAN LOGHEM, J. J., JR. Quelques expériences dans les recherches de groupes sanguins en Hollande. *Gynaecologia*, 130(5): 297–312. [Central Lab., Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherl.]

VAUGHAN, C. V. III, ALLEN, F. H. JR., & DIAMOND, L. K. Erythroblastosis fetalis. IV. Further observations on kernicterus. *Pediatrics* 6(5): 706–716. [3]

VECCHIO, F., & BARBAGALLO, E. Ricerche sierologiche sul potere antigene di taluni tipi di emoglobina umana normali e patologici. I. L'emoglobina dell'anemia di Cooley e dell'anemia drepanocitica. *Pediatria*, Nap. 58(7–8): 481–497.

WEINER, A. E., REID, D. E., ROBY, C. C. & DIAMOND, L. K. Coagulation defects with intrauterine death from Rh isosensitization. *Am. J. Obst.* 60(5): 1015–1022. [221 Longwood Ave., Boston, Mass.]

WELLER, C. G., ELLIOTT, W., & GUSMAN, A. R. Hereditary diabetes insipidus: unusual urinary tract changes. *J. Urol.* 64(5): 716–721. [12 Fox St., Aurora, Ill.]

WELLER, C. G., ELLIOT, W., & GUZMÁN, A. R. Alteraciones del tracto urinario en la diabetes insípida hereditaria. *Rev. méd. cubana*, 61(7): 469–475.

WEYDE, R. Naevus epithelioma-cylindromatosus, dominant nedarvet i fire generasjoner. *Nord. med.* 44(31): 1249–1252. [Norske Radium-hospital, Oslo, Norw.]

WIENER, A. S. Heredity and nomenclature of the Rh-Hr blood types. *Bull. World Health Org.* 3(2): 265–278. [64 Rutland Rd., Brooklyn 25, N. Y.]

WILLMER, E. N. Some aspects of colour-blindness. *Brit. M. J.* 2(4689): 1141–1145.

WITTERMANS, A. W., & SCHULTZ, B. Genealogischer Beitrag zur Frage der geheilten Schizophrenien. *Arch. Psychiat.*, Berl. 185(2): 211–232. [Huydecoperweg 27, Zeist, Netherl.]

ZOUTENDYK, A. The Rh factor; its present status. *S. Afr. M. J.* 24(48): 1002–1006 [S. Afr. Inst. for Med. Research, Johannesburg, S. Afr.]

ZUCKERMAN, S. Taxonomy and human evolution. *Biol. Rev. Cambridge Philos. Soc.* 25(4): 435–485. [Dept. Anatomy, Univ. Birmingham, Eng.]

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